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FORM PTO-1390 (REV. 5/93) U.S. Department of Commerce Patent and Trademark Office		Attorney's Docket Number 1721-13
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. Application No. (if known, see 37 C.F.R. 1.5) Unknown 09/214759
International Application No. PCT/FR97/01295	International Filing Date 11 July 1997	Priority Date Claimed 12 July 1996

Title of Invention

DNA AND SPECIFIC PROTEINS OR PEPTIDES OF THE *NEISSERIA MENINGITIDIS* SPECIES BACTERIA, METHOD FOR OBTAINING THEM AND THEIR BIOLOGICAL APPLICATIONS

Applicant(s) For DO/EO/US

NASSIF et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau
   c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. The above checked items are being transmitted:
    a. ☐ before the 18th month publication.
    b. ☐ after publication and the Article 20 communication but before 20 months from the priority date.
    c. ☐ after 20 months.
    d. ☒ by 30 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
    e. ☐ after 30 months.

    Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted (1) after 20 months and no proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date, or (2) after 30 months and a proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
12. At the time of transmittal, Amendments to the claims under Article 34
    a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
    b. ☐ have been transmitted by the International Bureau
    c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
    d. ☐ have not been made and will not be made.
13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____ , namely:

14. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
15. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
16. ☒ A **FIRST** preliminary amendment.
    ☐ A **SECOND** OR **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.

Attorney's Docket Number **1721-13**

19. ☒ Other items or information: **International Search Report and Form PTO-1449; Request and Notification & Preliminary Examination Report**

20. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5) -- Search Report has been prepared by the EPO or JPO .....$840.00 -- International preliminary examination fee paid to USPTO (37 CFR 1.492).....$670.00 -- No international preliminary examination fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00 -- Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00 -- International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provision of PCT Article 33(1) to (4).....$96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of $130.00 for furnishing the National fee or oath or declaration later than ☐ 20 ☒ 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE			
Total Claims	**32**	-20 =	12	X	$18.00	$	216.00
Independent Claims	**2**	-3 =	0	X	$78.00		0.00
Multiple Dependent Claims(s) (if applicable)				+$260.00		$	0.00

TOTAL OF ABOVE CALCULATIONS =	$	**1186.00**
Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28).		0.00
SUBTOTAL =	$	**1186.00**
Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☒ 30 mos., from the earliest claimed priority date (37 CFR 1.492(f).		130.00
TOTAL NATIONAL FEE =	$	**1316.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$	0.00
Fee for Petition to Revive Unintentionally Abandoned Application ($1,210 – Small Entity Fee = $605)	$	0.00
TOTAL FEES ENCLOSED =	$	**1316.00**
	Amount to be refunded	$
	Charged	$

a. ☒ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $_____ to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.

Signature

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36,663 — **January 12, 1999**
Registration Number — Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

NASSIF et al Atty. Ref.: **1721-13**

Serial No. **Unknown** Group:

Filed: **January 12, 1999** Examiner:

For: **DNA AND SPECIFIC PROTEINS OR PEPTIDES OF THE *NEISSERIA MENINGITIDIS* SPECIES BACTERIA, METHOD FOR OBTAINING THEM AND THEIR BIOLOGICAL APPLICATIONS**

* * * * * * * * * * *

January 12, 1999

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to calculation of the filing fee and in order to place the above identified application in better condition for examination, please amend the claims as follows:

IN THE CLAIMS

1. (Amended) DNAs, [characterized in that they are in all or part genes, with their] comprising a reading frame[, present in] of *Neisseria meningitidis* ([called] Nm [below]), but absent both from *Neisseria gonorrhoeae* ([called] Ng [below]) and from Neisseria Pactamica [sic] ([called] N1 [below]), with the exception of genes involved in the biosynthesis of the polysaccharide capsule, *frp*A, *frp*C, *opc*, *por*A, rotamase, the sequence IC1106 [sic], IgA proteases, pilin, pilC, proteins which bind transferrin and opacity proteins.

Claim 2, line 1, delete "characterized in that they" and insert -- which are --.

Claims 3, 4 and 5, lines 1 and 2 of each, delete "characterized in that they comprise" and insert -- comprising --.

Claims 6 and 7, line 1 of each, delete "characterized in that their" and insert -- comprising a --; and line 2 of each, after "sequence" insert -- which --.

Claim 8, line 1, delete "characterized in that they" and insert -- which --.

Claims 9 and 10, lines 1 and 2 of each, delete "characterized in that their sequence corresponds" and insert -- which correspond --.

Claim 11, line 1, delete "characterized in that they" and insert -- which --.

Claims 12 and 13, lines 1 and 2 of each, delete "characterized in that they comprise" and insert -- comprising --.

Claim 14, lines 1 and 2, delete "any one of the preceding claims, characterized in that it" and insert -- claim 1 which --.

Claim 15, lines 1 and 2, delete "any only of claims 1 to 14, characterized in that" and insert -- claim 1 wherein --.

Claim 16, lines 1 and 2, delete "any one of claims 1 to 15, characterized in that it" and insert -- claim 1 which --.

17. (Amended) Host cell, [more particularly bacterial cell or Nm cell,] transformed by insertion of at least one DNA according to [any one of claims 1 to 15] claim 1.

18. (Amended) Cell comprising genes or gene fragments specific to Nm, [more particularly bacterial cell or Nm cell,] the chromosome of which is deleted by at least one DNA according to [any one of claims 1 to15,] claim 1 in particular a DNA responsible for the pathogenicity.

19. (Amended) DNAs, [characterized in that their sequence] which corresponds in all or part to the transcription of at least one DNA sequence or sequence fragment according to [any one of claims 1 to 15] claim 1.

20. (Amended) Antisense nucleic acids, [characterized in that their] which have a sequence [corresponds] corresponding to the antisense of at least one nucleotide sequence according to [any one of claims 1 to 15 or 19,] claim 1 or a fragment of such a sequence, and in that they carry, where appropriate, at least one chemical substituent, such as a methyl group and/or a glycosyl group.

Claim 21, lines 3 and 4, delete "any one of claims 1 to 15 or 19," and insert -- claim 1 --.

Claim 22, lines 2 through 4, delete ", more specifically peptides corresponding to all or part of those coded by a DNA according to claim 14".

Claim 23, line 3, delete "20 or".

Claim 26, line 2, delete "or 25".

Claim 28, line 8, delete "one of claims 1 to 15 or 19" and insert -- claim 1 --.

Claim 29, lines 5 and 6, delete "any one of claims 21 or 22" and insert -- claim 21--.

30. (Amended) Kits for carrying out a method according to [any one of claims 28 or 29] claim 28, characterized in that they comprise

- at least one of said reagent [as defined in claim 28 or 29, that is to say of the nucleic acid, antibody or peptide type],

- products, in particular markers or buffers, which enable the intended nucleotide hybridization reaction or immunological reaction to be carried out, as well as use instructions.

31. (Amended) Vaccine composition including in its spectrum, in particular in combination with at least one childhood vaccine, antimeningococcal prophylaxis and intended for prevention of any form of infection by Neisseria meningitidis, characterized in that it comprises, in combination with (a) physiologically acceptable vehicle(s), an effective amount:

- of peptide according to claim 21 [or 22], or

- of an antibody or anti-antibody fragment [according to claim 23] thereto,

this material optionally being conjugated, in order to reinforce its immunogenicity, with a carrier molecule such as a poliovirus protein, tetanus toxin, protein produced by the hypervariable region of a pilin.

32. (Amended) Vaccine composition including in its spectrum, in particular in combination with at least one childhood vaccine, antimeningococcal prophylaxis and intended for prevention of any form of infection by Neisseria meningitidis, characterized in that it comprises, in combination with (a) physiologically acceptable vehicle(s), an effective amount:

- of nucleic acids according to [any one of claims 1 to 15 or 19] claim 1 or

- of cells [according to claim 17 or 18] containing same.

REMARKS

The above amendments are made to place the claims in a more traditional format.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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DNAs and proteins or peptides specific to bacteria of the species *Neisseria meningitidis*, processes for obtaining them and their biological uses.

The invention relates to DNAs and to proteins and peptides which are specific to bacteria of the species *Neisseria meningitidis* (abbreviated below to Nm), to the process for obtaining them and to their biological uses, in particular for the prevention and detection of meningococcal infections and meningitis.

It is known that Nm is one of the main agents of cerebrospinal meningitis.

Studies conducted in the United States have shown that 5 to 10% of the population are asymptomatic carriers of the Nm strain(s). The transmission factors of Nm are poorly known. For a proportion of persons infected, Nm penetrates the bloodstream, where it can cause meningococcaemia and/or progress to the cerebrospinal stream, to cause meningitis. Without fast antibiotic treatment, the infection can develop like lightning and become fatal.

Compared with other pathogens, Nm has the characteristic of being able to cross the haemato-encephalic barrier to colonize the meninges. The study of the pathogenicity of Nm is therefore important not only in the context of meningitis, but also in the context of any disease which affects the brain.

The benefit of having available tools specific to this species of bacteria for the uses envisaged above is therefore understood.

Genetically, Nm is very close to bacteria of the species *Neisseria gonorrhoeae* (abbreviated to Ng below) and of the species *Neisseria lactamica* (abbreviated to Nl below). However, their pathogenicity is very different.

Nm colonizes the nasopharynx, and then crosses the pharyngeal epithelium to invade the submucous space, thus being responsible for septicaemia and meningitis.

Ng is especially responsible for infections located in the genitourinary tract. It colonizes the genital mucosa, and then crosses the epithelium, subsequently invading the subepithelium, where it multiplies and is responsible for a severe inflammatory reaction. Disseminated gonococcal infections are possible, but remain rare and are the result of only some strains.

As regards Nl, it is considered that this is a non-pathogenic strain, since it is not responsible for a localized or general invasion.

A first consideration thus led to taking into account the fact that Nm and Ng, while being bacteria very close to one another, have different pathogenic potencies.

Since the genome of these bacteria has a high homology, only limited parts of the genome of Nm and Ng must code for specific virulence factors responsible for their pathogenesis.

It is clear that Nm has, compared with Ng, DNA sequences which are specific to it and which must be involved in the expression of its specific pathogenic potency.

The species Nm is subdivided into serogroups based on the nature of the capsular polysaccharides.

At least 13 serogroups have been defined, among which serogroups A, B and C are responsible for about 90% of meningitis cases. Groups A and C are found in epidemic forms of the disease. Group B is the serogroup generally isolated the most in Europe and the United States.

The capsule, which is present in Nm and absent from Ng, has served as the basis for formulating meningococcal antimeningitis vaccines.

The polysaccharides of the Nm capsule have been used to formulate a vaccine which has proved to be effective in preventing in adults the meningitis caused by meningococci of serogroups A, C, W135 and Y.

However, the polysaccharide of Nm group C has proved to be weakly immunogenic in children of less than two years, while the polysaccharide of Nm group B is non-immunogenic in man and shares epitopes with adhesion glycoproteins present in human neuronal cells.

There is therefore no universal vaccine capable of preventing infections caused by all the serogroups of the meningococci and capable of responding to the intrinsic antigenic variability of bacterial pathogens in general and Nm in particular.

Because of the cross-reactivity of the Nm group B polysaccharide with human antigens, the multiplicity of the serogroups and the antigenic variability of Nm, the strategies proposed to date cannot lead to a vaccine which is effective in all situations.

Research is therefore concentrated on study of the characteristic elements responsible for the specificity of the meningococcal pathogenesis.

The majority of genes which have been studied in either of the two bacteria Nm or Ng have their homologue in the second bacterium.

In the same way, the majority of virulence factors identified to date in Nm have a counterpart in Ng, that is to say pilin, the PilC proteins, the opacity proteins and the receptors of lactoferrin and transferrin.

The specific attributes of meningococci characterized in the prior art are the capsule, the Frp proteins analogous to RTX toxins, Opc proteins of the external member, glutathione

peroxidase, the porin PorA and the rotamase gene.

Among these, only the capsule is invariably present in the virulent strains of Nm. However, several extracellular pathogens have a capsule without nevertheless crossing the haemato-encephalic barrier.

Attributes which have not yet been identified must therefore be responsible for the specificity of the meningococcal pathogenesis. These attributes are probably coded by DNA sequences present among the meningococci but absent from the gonococci.

The inventors have developed a new approach based on subtractive isolation of Nm-specific genes, which genes must be linked to the specific pathogenesis of Nm, and more particularly to crossing of the haemato-encephalic barrier.

The subtractive method developed in the prior art has resulted in the production of epidemological [sic] markers for some Nm isolates. These markers are of limited use: they do not cover all the serogroups of the Nm species.

In contrast to these studies, the work of the inventors has led, by confronting Nm with the entire Ng chromosome sheared in a random manner, to the development of a means for cloning all the DNAs present in Nm and absent from Ng, thus providing tools of high specificity with respect to Nm, and thus enabling the genetic variability of the species to be responded to for the first time.

The terms "present" and absent" used in the description and claims in relation to the DNAs of a strain or their expression products are interpreted on the basis of identical hybridization conditions (16 h at 65ºC, with $NaPO_4$ 0.5 M, pH 7.2; EDTA-Na 0.001 M, 1%, 1% bovine serum albumin and 7% sodium dodecylsulphate) using the same probe and the same labelling intensity of the probe, the same amount of

chromosomal DNA and the same comparison element (chromosomal DNA of the homologous strain).

It is therefore considered that the DNA is present if the signal obtained with the probe is practically the same as that obtained with the reference strain.

Conversely, it is considered that the DNA is absent if this signal appears very weak.

A second consideration of the pathogenicities of Nm and Ng leads to taking into account their common capacity for colonization and penetration of the mucosa, and then invasion of the subepithelial space of the latter. It is highly probable that this process involves virulence factors common to the two pathogens. In this respect, it is known that a certain number of virulence factors have already been identified in Nm and in Ng, such as the pili proteins, PilC, the opacity proteins, the IgA proteases, the proteins for binding to transferrin and to lactoferrin, and the lipooligosaccharides.

The approach of the inventors is thus extended to investigation of the Nm regions which are specific to Nm and Ng but absent from the non-pathogenic species Nl, and in a general manner to investigation of the chromosomal regions of the DNAs and their expression products specific to a given species by the means developed in accordance with the invention.

The object of the invention is thus to provide DNAs of Nm specific to its pathogenic potency and means for obtaining them, in particular by formulating banks formed exclusively from these Nm-specific DNAs.

It also provides the products derived from these DNA sequences.

The invention also relates to the utilization of specific

and exhaustive characteristics of these banks to formulate tools which can be used, in particular, in diagnostics, treatment and prevention.

The DNAs of the invention are characterized in that they are in all or part genes, with their reading frame, present in *Neisseria meningitidis*, but absent both from *Neisseria gonorrhoeae* and from *Neisseria lactamica*, with the exception of genes involved in the biosynthesis of the polysaccharide capsule, frpA, frpC, opc, por A, rotamase, the sequence IS1106, IgA proteases, pilin, pilC, proteins which bind transferrin and opacity proteins.

As stated above, the terms "present" and "absent" are interpreted on the basis of the hybridization conditions used in the Southern blotting described in the examples and referred to above.

It can be seen that these DNAs include variants where these express a function intrinsic to the Nm species, more particularly a phenotype found solely in Nm or in common exclusively with Ng.

According to a main aspect, these DNAs are specific to the pathogenicity of *Neisseria meningitidis*, in spite of the genetic variability of this species.

According to an embodiment of the invention, the said DNAs are specific to Nm, in contrast to Ng.

More particularly, the Nm-specific DNAs are absent from *Neisseria lactamica* and from *Neisseria cinerea*.

Surprisingly, the majority of genetic differences between the strains of meningococci and those of gonococci appear grouped in distinct regions, which are said to correspond to the pathogenicity islets described previously for *E. coli* and *Y. pestis*.

In a preferred embodiment of the invention, these DNA are

thus also characterized in that they comprise one or more sequence(s) present on the chromosome of *Neisseria meningitidis* Z2491 between *tufA* and *pilT*, or region 1 of the chromosome, and/or the sequence(s) capable of hybridizing with the above sequence(s), with the proviso of being specific to *Neisseria meningitidis*.

"Specific" in the description and the claims means the nucleotide sequences which hybridize only with those of Nm under the hybridization conditions given in the examples and referred to above.

In this respect, it can be seen that, in a general manner, when "all or part" of a sequence is referred to in the description and claims, this expression must be interpreted with respect to the specificity defined above.

Furthermore, all or part of a peptide or a fragment of a peptide or an antibody means a product having the biological properties respectively of the natural peptide or the antibody formed against the peptide.

Genes of the *Neisseria meningitidis* capsule are grouped in region 1.

DNAs of this type have a sequence corresponding in all or part to SEQ ID No. 9, 13, 22 or 30, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or have a sequence which is capable of hybridizing with at least a fragment of any one of these sequences.

In another preferred embodiment of the invention, these DNA are also characterized in that they are made up of one or more sequence(s) present on the chromosome of *Neisseria meningitidis* Z2491 between *pilQ* and λ740, or region 2 of the chromosome, and/or the sequences(s) capable of hybridizing with the above sequence(s), with the proviso of being specific

to *Neisseria meningitidis*.

DNAs according to this embodiment have a sequence corresponding in all or part to SEQ ID No. 1, 2, 4, 6, 7, 10, 15, 31 or 34, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or have a sequence which is capable of hybridizing with at least a fragment of any one of these sequences.

The invention especially provides all or part of the DNA sequence SEQ ID No. 36 of 15,620 bp, and the sequences corresponding to the open reading frames SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44 and SEQ ID No. 45.

In yet another preferred embodiment of the invention, these DNAs are also characterized in that they are made up of one or more sequence(s) present on the chromosome of *Neisseria meningitidis* Z2491 between *argF* and *opa*B, or region 3 of the chromosome, and/or the sequence(s) capable of hybridizing with the above sequence(s), with the proviso of being specific to *Neisseria meningitidis*.

DNAs according to this embodiment are characterized in that they have a sequence corresponding in all or part to SEQ ID No. 8, 21, 23, 25, 26, 28, 29, 32 or 35, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or have a sequence which is capable of hybridizing with at least a fragment of any one of these sequences.

Regions 1, 2 and 3 identified above have a high proportion of sequences specific to *Neisseria meningitidis* and also fall within the context of the invention.

Other DNAs representative of the specificity with respect to *Neisseria meningitidis* have one or more sequences which is/are present on the chromosome of *Neisseria meningitidis*

Z2491 but are not part of regions 1, 2 and 3 defined above.

Such DNAs comprise one or more sequence(s) corresponding in all or part to SEQ ID No. 3, 5, 11, 12, 14, 16, 18, 19, 20, 24, 27 or 33, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or have a sequence capable of hybridizing with such sequences.

Taking into account the uses envisaged in particular, the invention more specifically relates to the above DNAs involved in the pathogenesis of the bacterial organism.

In particular, it provides the DNAs corresponding to at least one of the characterizations given above and coding for a protein exported beyond the cytoplasmic membrane, and/or of which all or part of their sequence corresponds to the conserved region of the said DNAs.

According to another embodiment of the invention, the DNAs are thus common with those of Ng, but are absent from those of Nl.

These are more specifically the DNAs which are present on region 4 (arg J to reg F) or on region 5 (lambda 375 marker to pen A) on the chromosome of Nm Z2491 and/or are capable of hybridizing with the said DNAs present, with the proviso of being specific to Nm and Ng, in contrast to Nl.

"Specific to Nm and Ng in contrast to Nl" means the DNAs which hybridize with the DNAs of Nm and Ng under the hybridization conditions of the examples (see example 4 in particular).

The DNAs of regions 4 and 5 and those capable of hybridizing with these DNAs, with the proviso of expressing the intrinsic functions of Nm, have the advantage of intervening in a significant manner in the virulence of Nm, being involved in the stage of initial colonization and

penetration and in the septicaemic dissemination.

According to other embodiments, the invention provides transfer and expression vectors, such as plasmids, cosmids or bacteriophages, comprising at least one DNA as defined above.

It also provides host cells transformed by at least one DNA as defined above.

Other host cells of the invention comprise genes or gene fragments specific to Nm, and are characterized in that their chromosome is deleted by at least one DNA according to the invention, in particular a DNA responsible for the pathogenicity. They are more specifically bacterial cells, in particular of Nm.

The invention also relates to the RNAs of which the sequence corresponds in all or part to the transcription of at least one DNA sequence or sequence fragment as defined above.

The invention also relates to the antisense nucleic acids of the DNAs as defined above, or of fragments of these DNAs.

These antisense nucleic acids carry, where appropriate, at least one substituent, such as a methyl group and/or a glycosyl group.

Other products which fall within the context of the invention include polypeptides.

These polypeptides are characterized in that they have an amino acid chain corresponding to all or part of a sequence coded by the nucleic acids defined above, or deduced from sequences of these nucleic acids.

They are advantageously polypeptides corresponding to all or part of the polypeptides exported beyond the cytoplasmic membrane, more specifically polypeptides corresponding to all or part of those coded by a conserved region.

As a variant, the polypeptides of the invention can be modified with respect to those corresponding to the nucleic

acid sequences such that they are particularly suitable for a given use, in particular use as a vaccine.

Modification is understood as meaning any alteration, deletion or chemical substitution where this does not affect the biochemical properties of the corresponding natural polypeptides, more specifically of functional proteins exported at the periplasm and the external membrane.

Other products according to the invention include antibodies directed against the above polypeptides.

The invention thus provides polyclonal antibodies, and also monoclonal antibodies, characterized in that they recognize at least one epitope of a polypeptide as described above.

It also relates to fragments of these antibodies, more particularly the fragments Fv, Fab and Fab'2.

The invention also relates to the anti-antibodies which are capable of recognizing the antibodies defined above, or their fragments, by a reaction of the antigen-antibody type.

According to the invention, the various products considered above are obtained by a synthesis and/or biological route in accordance with conventional techniques.

The nucleic acids can also be obtained from banks made up of Nm-specific DNAs such as are formulated by a subtractive technique, this technique comprising:

- mixing of two DNA populations,
- realization of at least one subtractive hybridization-amplification iteration, and
- collection of the desired DNA or DNAs, followed, where appropriate, by its/their purification with elimination of redundant sequences.

According to the invention, the two DNA populations originate respectively from a strain of *Neisseria*

meningitidis, the so-called reference strain for which the specific bank must be constructed, and a strain of *Neisseria*, the so-called subtraction strain, having a homology in primary DNA sequences of greater than about 70% with the *Neisseria meningitidis* strain, the DNA sequences of the subtraction and reference strains being obtained respectively by random shearing, and by cleavage by a restriction endonuclease capable of producing fragments less than about 1 kb in size.

The invention provides in particular a process for obtaining *Neisseria meningitidis*-specific DNA banks, comprising the stages of

- random shearing of the chromosomal DNA of a strain of *Neisseria gonorrhoeae*, the so-called subtraction strain, in particular by repeated passage through a syringe,

- cleavage of the chromosomal DNA of a strain of *Neisseria meningitidis*, the so-called reference strain, preferably by a restriction enzyme producing fragments less than about 1 kb in size,

- splicing of the DNA fragments of the reference strain, cleaved by the restriction enzyme, with suitable oligonucleotide primers,

- realization of a subtractive hybridization-amplification iteration, by:

. mixing of the two DNA populations under suitable conditions for hybridization of homologous sequences, and then

. amplification of auto-reannealed fragments and collection of these fragments,

. digestion of these fragments by a restriction enzyme and re-splicing with oligonucleotide primers, followed by a

- purification of the spliced DNA and, where appropriate, a new iteration of the subtractive hybridization, comprising mixing of DNA fragments of *Neisseria gonorrhoeae* sheared as

indicated above with DNA fragments of *Neisseria meningitidis* produced by the preceding iteration, followed, if desired, by cloning of the DNAs of the bank.

The primers used are oligodeoxynucleotide primers which are suitable for the restriction endonuclease used and allow insertion into a cloning site, such as the EcoRI site of the plasmid pBluescript. Such primers will advantageously be chosen among the oligodeoxynucleotides referred to in the sequence listing under SEQ ID no. 36 to 45.

The banks thus obtained are formed from DNAs which are specific to meningococci and absent from gonococci.

The specificity of the DNAs was verified, as described in the examples, at each iteration by Southern blots, with genes common to the subtraction strain and to the reference strain, or with the total DNA of each of the strains digested by a restriction endonuclease, such as *Cla*I.

At each iteration, the exhaustivity of the DNA bank was also verified by Southern blotting with probes known to be specific to the reference strain, that is to say for *Neisseria meningitidis* the *frp, opc* and rotamase genes in particular.

The experiments carried out showed that the banks obtained by the process of the invention are deficient in genes having a significant homology with species of Neisseria other than *Neisseria meningitidis*, for example the *ppk* or *pil*C1 genes, generally in only 2 or 3 iterations.

If necessary, two routes, which are not exclusive of each other, can be taken.

It is possible to proceed with an $(n+1)^{th}$ iteration using the DNA of iteration n as the DNA population of the reference strain.

As a variant, a second bank independent of the first is constructed, with a restriction enzyme of different

specificity to that used in the first bank, for example *MboI*.

In all cases, it is preferable to keep each of the products produced by each of the iterations performed.

The invention also provides the use of the subtractive technique described above to obtain banks of the DNAs common to Nm and Ng, but specific with respect to Nl.

Three different banks are advantageously constructed, two of them by digestion of the chromosomal DNA of Nm by *MboI* and *Tsp5091*, and the third by digestion of the chromosomal DNA of Nm with *MspI*. Two subtraction series allow the DNAs having the required specificity to be collected, as described in the examples.

The invention also relates to the process for obtaining these banks and the banks themselves.

It can be seen that, generally, the process of the invention can be used to obtain banks of DNAs specific to a given cell species, or to a given variant of the same species, where another species or another variant which is close genomically and expresses different pathogenic potencies exists.

Using the process of the invention, DNA banks specific to given species of cryptococci, *Haemophilus*, pneumococci or also *Escherichia coli*, or more generally any bacterial agent belonging to the same species and having different pathovars will advantageously be constructed.

Furthermore, from these banks the invention provides the means to have available virulence factors specific to a species or a given variant.

Such banks are therefore tools which are of great interest for having available attributes which are responsible for the specificity of a pathogen, this use being more specifically illustrated according to the invention by the

obtaining of banks comprising the attributes responsible for the specificity of the meningococcal pathogenesis.

Study of the products of the invention, the nucleic acids, polypeptides and antibodies, has enabled an absolute specificity with respect ot *Neisseria meningitidis*, regardless of the strain and its variability, to be demonstrated.

These products are therefore particularly suitable for diagnosis or prevention of infections and meningitis caused by *Neisseria meningitidis*, whether in adults or children and regardless of the serogroups of the strain in question.

The method for diagnosis, according to the invention, of a meningococcal infection, and more particularly of meningococcal meningitis, by demonstration of the presence of *Neisseria meningitis* in an analytical sample is characterized by the stages of:

- bringing into contact a sample to be analysed, that is to say a biological sample or a cell culture, and a reagent formulated from at least one nucleic acid as defined above, if appropriate in the form of a nucleotide probe or a primer, or, as a variant, from at least one antibody or a fragment of an antibody as defined above, under conditions which allow, respectively, hybridization or a reaction of the antigen-antibody type, and

- detection of any reaction product formed.

If the reagent is formulated from a nucleic acid, this can be in the form of a nucleotide probe in which the nucleic acid or a fragment of the latter is labelled in order to enable it to be detected. Suitable markers include radioactive, fluorescent, enzymatic or luminescent markers.

As a variant, the nucleic acid is included in a host cell, which is used as the reagent.

In these various forms, the nucleic acid is used as such

or in the form of a composition with inert vehicles.

If the reagent is compiled from an antibody, or a fragment of an antibody, this can be labelled for detection purposes. Most generally, a fluorescent, enzymatic, radioactive or luminescent marker is used.

The antibody or the antibody fragment used, which is labelled if appropriate, can be used as such or in the form of a composition with inert vehicles.

The sample used in the stage of bringing the components into contact is a biological sample produced by a mammal, such as cephalorachidian fluid, urine, blood or saliva.

The detection stage is carried out under conditions which allow the reaction product to be demonstrated when it is formed. Conventional means use fluorescence, luminescence, colour or radioactive reactions, or also autoriadography [sic] techniques. It is also possible to quantify the product.

The invention also relates to the labelled products, the nucleic acids and antibodies, as new products.

The method defined above can be used for diagnosis of an immune reaction specific to a meningococcal infection.

The reagent used is thus a polypeptide according to the invention, as coded by the said nucleic acid sequences, corresponding to the natural product or a polypeptide which is modified but has the biological and immunological activity of the corresponding natural polypeptide.

It is advantageously a polypeptide exported beyond the cytoplasmic membrane of *Neisseria meningitidis*, more particularly the part of such a polypeptide corresponding to the conserved region of the DNA.

The invention also relates to kits for carrying out the methods defined above. These kits are characterized in that they comprise:

- at least one reagent as defined above, that is to say of the nucleic acid, antibody or polypeptide type,

- products, in particular markers or buffers, which enable the intended nucleotide hybridization reaction or immunological reaction to be carried out, as well as use instructions.

The specificity of the products of the invention and their location on the chromosome of *Neisseria meningitidis* Z2491, either grouped in a region and able to be interpreted as pathogenicity islets, or isolated on the chromosome, impart to them a very particular interest for realization of vaccine compositions with a universal purpose, that is to say whatever the strain and the variability which it expresses. These compositions can include in their spectrum other prophylaxes, and can be, for example, combined with childhood vaccines.

The invention thus provides vaccine compositions which include in their spectrum antimeningococcal prophylaxis, intended for prevention of any infection which may be caused by *Neisseria meningitidis*, these compositions being characterized in that they comprise, in combination with (a) physiologically acceptable vehicle(s), an effective amount of polypeptides or anti-antibodies or their fragments as defined above, these products optionally being conjugated, in order to reinforce their immogenicity [sic].

Immunogenic molecules which can be used comprise the poliovirus protein, the tetanus toxin, or also the protein produced by the hypervariable region of a pilin.

As a variant, the vaccine compositions according to the invention are characterized in that they comprise, in combination with (a) physiologically acceptable vehicle(s), an effective amount:

- of nucleic acids as defined above,

- of transformed host cells as defined above, or

- of Nm cells, the chromosome of which has been deleted by at least one DNA sequence according to the invention involved in the pathogenicity of the bacterium. The nucleotide material used is advantageously placed under the control of a promoter of its expression in vivo and synthesis of the corresponding protein. To reinforce the immunogenicity, it is also possible to combine this nucleic material with a DNA or an RNA which codes for a carrier molecule, such as the poliovirus protein, tetanus toxin or a protein produced by the hypervariable region of a pilin.

The vaccine compositions of the inventions can be administered parenterally, subcutaneously, intramuscularly or also in the form of a spray.

Other characteristics and advantages of the invention are given in the examples which follow for illustration thereof, but without limiting its scope.

In these examples, reference will be made to figures 1 to 11, which show, respectively,

- figures 1A, 1B, 1C, 1D, 1E, 1F and 1G: analysis of the subtractive bank *Tsp*5091,

- figure 2: the distribution of the Nm-specific sequences, in contrast to Ng, on the chromosome of the strain Z2491 (left-hand part) and of Nm-specific sequences, in contrast to Nl (right-hand part),

- figure 3A to 3C: the reactivity of the clones of the 3 regions of the chromosome according to the invention towards a panel of strains of the genus *Neisseria*,

- figure 4: the position in region 2 of the chromosome of Nm of oligonucleotides used as probes,

- figures 5, 6 and 7: the Southern blots of a panel of strains of the genus *Neisseria*, using parts of region 2 of Nm as

probes,

- figures 8A to 8C: the Southern blots with 3 subtractive banks over a panel of 12 strains of *Neisseria*, and

- figures 9, 10 and 11: the reactivity of clones of the 3 subtractive banks with respect to Nm, Nl and Ng.

In the examples which follow, the following materials and methods were used:

Bacterial strains - To obtain the subtractive banks, strain Z2491 of Nm (Achtman *et al.*, 1991, *J. Infect. Dis.* 164, 375-382), the strains MS11 (Swanson *et al.*, 1974, *Infect. Immun.* 10, 633-644) and the strains 8064 and 9764 of Nl were used, it being understood that any other strain of the species in question could be used.

In order to verify the specificity of these banks, 6 strains of Nm, 4 strains of Ng, one strain of Nl (*Neisseria lactamica*) and one strain of Nc (*Neisseria cinerea*) were used.

The six strains of Nm are: Nm Z2491 of serogroup A, Nm 8013 of serogroup C (XN collection), Nm 1121, no serogrouping possible (XN collection), Nm 1912 serogroup A (XN collection), Nm 7972 of serogroup A (XN collection) and Nm 8216 of serogroup B (XN collection).

The four strains of Ng are: Ng MS11 (Pasteur Institute, Paris), Ng 403 (Pasteur Institute, Paris), Ng 6934 (Pasteur Institute, Paris), Ng WI (isolated from a disseminated gonococcal infection), Ng 4Cl, Ng 6493 and Ng FA 1090.

The strains of Nl are Nl 8064 and Nl 9764 (XN collection), and that of Nc is Nc 32165 (XN collection).

Molecular genetics techniques

Unless indicated otherwise, the techniques and reagents used correspond to those recommended by Sambrook *et al* (Sambrook *et al* 1989, Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press). The

oligodeoxynucleotides used in this study are:

RBAm12, 3'AGTGGCTCCTAG 54 (SEQ ID No. 54)
RBam24, 5' AGCACTCTCCAGCCTCTCACCGAG 3'; (SEQ IN No. 55)
Jbam12, 3' GATCCGTTCATG 5'; (SEQ ID No. 60)
JBAM24, 5' ACCGACGTCGACTATCCATGAACG 3'; (SEQ ID No. 61)
REco12, AGTGGCTCTTAA; (SEQ ID No. 56)
REco24, 5' AGCACTCTCCAGCCTCTCACCGAG 3'; (= RBam 24)
JEco12, GTACTTGCTTAA; (SEQ ID No. 62)
JEco24, 5' ACCGACGTCGACTATCCATGAACG 3'; (= JBam24)
NEco12, AATTCTCCCTCG; (SEQ ID No. 64)
NEco24, AGGCAACTGTGCTATCCGAGGGAG; (SEQ ID No. 65).

Transfer to membranes (Southern blots)

The transfers to membranes were effected by capillary transfers to positively charged nylon membranes (Boehringer Mannheim). The hybridizations were carried out at 65ºC in a solution comprising NaPi [sic] 0.5 M pH 7.2/EDTA 1 mM/SDS 7%/BSA 1%. The membranes were washed in a solution comprising NaPi [sic] 40 mM pH 7.2/EDTA 1 mM/SDS 1%. The final washing was carried out at 65ºC for 5 min.

The probe *frp* obtained with oligonucleotides based on the *frp*A sequence corresponds to 2.4 kb of the 5' end of the gene of the strain Z2491. The *opc* and rotamase probes corresponding to whole genes are produced from the strain Z2491 using oligonucleotides constructed on the basis of published sequences. The probes *pilC1* and *ppk* (polyphosphate kinase) correspond to inserts of the plasmids pJL1 and pBluePPK6001 respectively.

<u>Example 1: Construction of banks of DNAs present in Nm and absent from Ng.</u>

a. "*MboI*" bank

Construction - The DNA of Nm Z2491 was cleaved by the endonuclease *Mbo*I and subjected to two iterations of a method called CDA (comprehensive difference analysis) below. This method comprises subtractive hybridization in the presence of excess sheared DNA of Ng MS11 and amplification by PCR of those meningococcal sequences which, since they are absent from or do not have significant homology with the DNA of Ng MS11, could reanneal

The chromosomal DNA of the strain Ng MS11 is sheared randomly by repeated passage through a hypodermic syringe until fragments of a size ranging from 3 to 10 kb are obtained. These DNA fragments are purified by extraction with phenol.

The chromosomal DNA of the strain Nm Z2491 is itself cleaved by the restriction endonuclease *Mbo*I. These DNA fragments (20 µg) are spliced with 10 nmol of annealed oligonucleotides RBam12 and RBam24. The excess primers are removed by electrophoresis over 2% agarose gel of low melting point. The part of the gel containing amplified fragments greater than 200 bp in size is excised and digested by β-agarase. These fragments are purified by extraction with phenol.

To carry out a subtractive hybridization (first iteration), 0.2 µg of the Nm DNA spliced with the RBam oligonucleotides is mixed with 40 µg Ng DNA in a total volume of 8 ml of a buffer EE 3X (a buffer EE 1X is composed of N-(2-hydroxyethyl)piperazine-N'-(3-propanesulphonic acid) 10 mM and EDTA 1 mM, and its pH is 8.0). This solution is covered with mineral oil and the DNA is denatured by heating at 100ºC for 2 min. 2 µl NaCl 5 M are added and the mixture is left to hybridize at 55ºC for 48 h. The reaction mixture is diluted to

1/10 in a preheated solution composed of NaCl and buffer EE, and in then immediately placed on ice.

10 µl of this dilution are added to 400 µl of PCR reaction mixture (Tris.HCl pH 9.0 10 mM; KCl 50 mM; $MgCl_2$ 1.5 mM; Triton X100 0.1%; 0.25 mM of each of the four triphosphate deoxynucleotides; Taq polymerase 50 units per ml). The mixture is incubated for 3 min at 70ºC to complete the ends of the reannealed meningococcal DNA fragments.

After denaturing at 94ºC for 5 min and addition of the oligonucleotide RBam24 in an amount of 0.1 nmol per 100 µl, the hybridizations are amplified by PCR (30 cycles of 1 min at 94ºC, 1 min at 70ºC and 3 min at 72ºC, followed by 1 min at 94ºC and 10 min at 72ºC; Perkin-Elmer GeneAmp 9600).

The amplified meningococcal fragments are separated from the primers and high molecular weight gonococcal DNAs on gel. They are digested by *Mbo*I and the oligonucleotides JBam12 and JBam 24 are spliced to them again. These spliced DNAs are again purified over gel and extracted with phenol.

A second iteration of the subtractive hybridization is carried out on 40 µg of the randomly sheared Ng DNA and 25 ng of the DNA spliced with the JBam oligonucleotides obtained from the first iteration of the subtractive hybridization. During this second iteration, amplification of the auto-annealed Nm DNA is effected with the aid of the oligonucleotide JBam24.

Specificity - In order to confirm their Nm specificity, the amplified sequences after the second iteration of the CDA method are labelled and used as a probe for the DNA digested by *Cla*I produced from a panel of six strains of *Neisseria meningitidis*, four of *Neisseria gonorrhoeae*, one of *Neisseria lactamica* and one of *Neisseria cinerea*.

The Southern blots obtained show that the amplified

sequences resulting from the second iteration of the CDA method have a high reactivity with several bands corresponding to meningococci, and do not have a reactivity with the bands corresponding to the Ng, Nl and Nc strains.

The "MboI" bank thus appears to be Nm-specific.

Exhaustivity - In order to test the exhaustivity of the bank, all the products produced from the first and second iterations of the CDA method and also the initial chromosomal materials of Nm Z2481 [sic] and Ng MS11 are subjected to agarose gel electrophoresis, transferred to a membrane and brought into contact with probes comprising genes known to be meningococcus-specific, that is to say *frp*, *opc* and rotamase (Southern blotting).

As a result of these hybridizations, the Nm-specific gene *frp* is represented in the *Mbo*I bank by a fragment of 600 bp, but no activity is observed for the rotamase and *opc* genes. The *Mbo*I bank, although Nm-specific, therefore cannot be considered exhaustive.

Given their high specificity, the fragments produced by the second iteration of the CDA method for the *Mbo*I bank can nevertheless be cloned on the *Bam*HI site of the plasmid pBluescript.

A sequence corresponding to any of the Nm-specific genes can be included in the subtractive bank only if it is carried by a restriction fragment of appropriate size. This condition is a function of two factors. Firstly, the probability that the largest fragments are entirely Nm-specific is low. Secondly, even if such fragments existed, they would be under-represented in the bank because of the limitations of the PCR technique, the amplification effectiveness of which decreases with increasing size of the fragments. Fragments greater that about 600 bp in size are not included in the bank. Because of

the absence of *Mbo* fragments of suitable size from the chromosome of Nm Z2491, the rotamase and *opc* genes cannot be included in the bank. Any enzyme cannot by itself produce a small fragment corresponding to any Nm-specific gene. A second bank was therefore constructed using another restriction enzyme with a different specificity: *Tsp*509 [sic].

b. "Tsp5091" bank

Construction - The enzyme *Tsp*5091 has the advantage of producing fragments of smaller size (less than about 1 kb) than the enzyme *MboI*.

*Tsp*509I recognizes the sequence AATT and leaves, projecting at 5', a sequence of 4 bases compatible with *Eco*RI. The oligonucleotides used are Reco, Jeco and NEco.

The method followed conforms with that followed for construction of the "*Mbo*I" bank described above. However, higher quantities of meningococcal DNA were used for the first iteration of the subtractive hybridization in order to compensate for the higher number of fragments of low molecular weight produced by *Tsp*509I. For the first iteration, 400 ng Nm DNA fragments and, in the second, 25 ng Nm fragments are subjected to subtractive hybridization with 40 µg randomly sheared Ng DNA.

For the construction of this "*Tsp*509I" bank, as a control, a third iteration of the subtractive hybridization is carried out using 40 µg sheared Ng DNA and 0.2 ng Nm fragments resulting from a digestion by *Tsp*509I and a resplicing, with NEco adaptors, of the fragments obtained as a result of the second iteration.

Specificity - As described for the previous bank, the product resulting from the second iteration of the CDA method is labelled and used as the probe for a panel of strains of

Neisseria.

Figure 1A illustrates the Southern blot hybridization of products of the second iteration of the CDA method with the DNA digested by *C1aI* of: Nm in track a, Ng MS11 in track b, Nm 8013 in track c, Ng 403 in track d, Nm 1121 in track e, Ng 6934 in track f, Nm 1912 in track g, Ng WI (strain DGI) in track h, Nm 7972 in track i, Nl 8064 in track j, Nc 32165 in track k, Nm 8216 in track l.

In contrast to the high reactivity observed with all the Nm strains, a low or no reactivity is observed with the Ng, Nl and Nc strains.

The specificity of the bank was studied earlier by reacting membrane transfers (Southern blots) of the products produced by each of the three iterations of the CDA method with probes corresponding to *pilC*1 and *ppk*. These two genes are common to Nm and Ng.

Figure 1B shows an agarose gel after electrophoresis of the chromosomes of Nm Z2491 and Ng Ms11, digested by *Tsp*509 [sic], and products resulting from each of the iterations of the CDA method.

In track a 1 µg of the chromosome of Nm was deposited, in track b 1 µg of that of Ng, in track c 0.15 µg of the products resulting from the first CDA iteration, in track d 0.1 µg of those of the second iteration, in track e 0.05 µg of the third iteration, MW representing the molecular size markers.

Figures 1C and 1D show gels obtained as described in figure 1B after transfer to the membrane (Southern blots) and hybridization with *pilC*1 (figure 1C) and *ppk* (figure 1D).

At the end of the second iteration of the CDA method, the sequences corresponding to the *pilC*1 and *ppk* genes are completely excluded from the bank.

Exhaustivity - The exhaustivity of the bank was examined

by reacting the products resulting from the subtractive hybridization with the probes corresponding to three Nm-specific genes (*frp*, rotamase and *opc*).

These Nm-specific probes react with the amplification products resulting from the first and second iteration of the subtractive hybridization.

Figures 1E, 1F and 1G show gels obtained as described in figure 1B after transfer to the membrane (Southern blots) and hybridization with *frp*A (figure 1E), rotamase (figure 1F) and *opc* (figure 1G).

However, a third iteration of the subtractive hybridization leads to the loss of Nm-specific sequences, since the fragments which react with the rotamase and *opc* genes are absent from this third iteration.

In consideration of all these data, it emerges that the products resulting from the second iteration of the CDA method are Nm-specific and also constitute an exhaustive bank of Nm-specific sequences.

The products resulting from this second iteration are cloned at the *Eco*RI site of the plasmid pBluescript.

The bank produced by *Tsp*509I is more exhautive [sic] than the bank produced by *Mbo*I, as the theory considerations based on the enzymatic production of smaller restriction fragments would suggest.

In accordance with this aspect, it should be noted that the *Tsp*509I bank is less redundant than the *Mbo*I bank, that is to say it comprises less duplication of clones. 86% of the clones of the *Tsp*509I bank correspond to distinct sequences, while only 43% of the clones correspond to distinct sequences in the *Mbo*I bank (data not shown).

The bank produced by *Tsp*509I thus constitutes a source of Nm-specific clones.

Example 2: Analysis of the clones of the subtractive bank

Cloning and sequencing of the Nm-specific DNAs

The DNAs of the subtractive banks are clones at the *Bam*HI (*Mbo*I bank) or *Eco*RI (*Tsp*509I bank) site of the plasmid pBluescript, and then transformed in DH5α of *E. coli*. The inserts are amplified by PCR carried out on the transformed colonies using the primers M13-50 and M13-40, the latter primer being biotinylated on its 5' end.

Sequencing was carried out on each PCR product after separation of the biotinylated and non-biotinylated strands using the system of Dynabeads M-280 with streptavidin (Dynal, Oslo). The sequences are screened according to their homologies with previously published sequences using the computer programs Blastn and Blastx (NCBI, USA and Fasta).

The PCR products resulting from the transformed bacteria colonies after using the primers M13-40 and M13-50 as described above were labelled by incorporation with random priming of α-^{32}P-dCTP and were used as a probe for the membrane transfers of the chromosomal DNA digested by *Cla*I of strains Nm Z2491 and Ng MS11, as described above, in order to verify their specificity.

Mapping of clones on the chromosome of the strain Nm Z2491.

The results of studies carried out with 17 clones of the "*Mbo*I" bank (designated by the letter B) and 16 clones of the "*Tsp*5091" bank (designated by the letter E), each of these clones having a unique sequence and being without counterpart in Ng, are reported.

The positions of the DNA sequences corresponding to cloned Nm-specific products were determined with respect to

the published map of the chromosome of Nm Z2491 (Dempsey *et al.* 1995, J. Bacteriol. 177, 6390-6400) and with the aid of transfers to membranes (Southern blots) of agarose gel subjected to pulsed field electrophoresis (PFGE).

The Nm-specific clones are used as probes for a hybridization on membranes (Southern blots) of the DNA of Nm Z2491 digested with enzymes of rare cutting sites, that is to say *Pac*I, *Pme*I, *Sgf*I, *Bgl*II, *Spe*I *Nhe*I and *Sgf*I.

The gels (20 x 20 cm) were gels of 1% agarose in a buffer TBE 0.5X and were subjected to electrophoresis at 6 V/cm for 36 hours according to pulsation periods varying linearly between 5 and 35 seconds.

The hybridizations on the membrane (Southern blots) were carried out as described above.

The results obtained are shown on figure 2: the reactivity was located by comparison with the positions of the fragments of corresponding size on the published map. The positions of all the genetic markers mapped by Dempsey *et al* (mentioned above) are visualized with the aid of points on the linear chromosomal map. The Nm-specific genes disclosed previously are labelled with an asterisk. The two loci called "*frp*" correspond to the *frp*A and *frp*C genes. The "*pilC*" loci correspond to the *pilC1* and *pilC2* genes, which are pairs of homologous genes and are not distinguished on the map. The accuracy of the positions of the Nm-specific clones of the invention depends on the overlapping of reactive restriction fragments. On average, the position is +/- 20 kb.

This mapping reveals a non-random distribution of the Nm-specific sequences. The majority of the Nm-specific sequences belong to three distinct groups. One of these groups (region 1) corresponds to the position of genes relating to the capsule which have been described previously.

A distinction is made between:

- E109, E138, B230 and B323 as being region 1,

- B322, B22O, B108, B132, B233, B328, E139, E145 as B101 as being region 2, and

- B306, E114, E115, E124, E146, E120, E107, E137 and 142 as being region 3.

63% of the sequences identified as specific to meningococci are located inside these three distinct regions.

This grouping contrasts with the distribution of previously disclosed Nm-specific genes (*frp*A, *frp*C, *por*A, *opc* and the region relating to the capsule).

This prior art would suggest in fact that the Nm-specific genes, with the exception of functional genes relating to the capsule, were dispersed along the chromosome.

Mapping of Nm-specific sequences on the chromosome leads to an unexpected result with regard to the prior art.

The majority of the genetic differences between the meningococcal and gonococcal strains tested are grouped in three distinct regions.

Meningococcal genes relating to the capsule are grouped in region 1.

The function of genes of the other regions is unknown, but homologies with published sequences (table 1) suggest similarities between certain genes of region 3 and bacteriophage transposase and regulatory proteins. No meningococcal virus has been characterized and it is tempting to think that these sequences are of phagic origin. Interestingly, the genome of H. *influenzae* also contains a sequence homologous to that of the Ner regulatory protein of phage Mu, but it is not known if it is a functional gene.

The clone B208 has a high homology (48% identical, 91% homology for 33 amino acids) with a clone of conserved regions

(field III) in the class of proteins which bind to TonB-dependent ferric siderophors.

The proximity of this clone with the Nm-specific *porA* genes and the *frp* genes regulated by iron, and in particular the possibility that it is an Nm-specific receptor protein exposed on the external membrane in itself is a good candidate for further research.

The clone B339 corresponds to the Nm-specific insertion sequence IS*1106*.

The low homology between the clone B134 and the *Aeromonas* insertion sequence and also the presence of multiple copies of the clone B134 among the various strains of Nm suggest that it could be a new type of Nm-specific insertion sequence.

The possibility that the regions containing the Nm-specific clones could correspond to pathogenicity islets as described previously for *E. coli* and *Y. pestis* is of particular interest.

The clones isolated in this invention will allow better understanding of the relevance of Nm-specific regions in allowing cloning and sequencing of larger chromosomal fragments, and directly by their use for loci mutations.

Finally, detection of meningococcus-specific genes possibly involved in the pathogenicity of the organism allows targeting of suitable antigens which can be used in an antimeningococcal vaccine.

The effectiveness and the speed of the method according to the inventions enables it to be used in a large number of situations for which the genetic differences responsible for a phenotype peculiar to one of 2 close pathogens are investigated.

Study of the reactivity of the clones of regions 1, 2 and 3 towards a panel of strains of *Neisseria*.

The PCR products corresponding to inserts of each of the clones were collected and used as probes for hybridization on membranes (Southern blots) for a panel of strains of Nm, Ng, Nl and Nc.

Regions 1 and 2 produce a limited number of bands for each of the meningococci. This suggests that these regions are both Nm-specific and common to all the meningococci.

Figure 3 illustrates the reactivity of the clones of regions 1, 2 and 3 towards a panel of neisserial strains. The clones of regions 1 (figure 3A), 2 (figure 3B) and 3 (figure 3C) taken together were used as probes towards a panel of meningococci, gonococci and towards a strain of Nl and Nc.

The tracks are as follows: DNA of: Nm Z2491 in track a, of Ng MS11 in track b, of Nm 8013 in track c, of Ng 403 in track d, of Nm 1121 in track e, of Ng 6934 in track f, of Nm 1912 in track g, of Ng WI (strain DGI) in track h, of Nm 7972 in track i, of Nl 8064 in track j, of Nc 32165 in track k, and of Nm 8216 in track l.

Remarkably, region 3 has reactivity only with the meningococci of serogroup A. This region 3 is therefore specific to a sub-group of Nm.

A comparison was made with the known sequences in the databanks in order to evaluate the possible functions of the cloned regions.

Table 1 which follows gives the positions of specific clones on the chromosomal map and the homologies with known sequences.

TABLE 1 - Position of specific clones on the chromosomal map and homologies with known sequences

			Reactive fragments						
Name of clone*	Size of insert	Pac	Pmc	Bgl	Spe	Nhe	Sgf	Position on Z2491	Homologies of protein sequences
B305	259	18-20	15-17	22-23	18	11-13	2	λ736	
B333	235		15-17	22-23	18	11-13	2	λ736	
E109[1+]	211		6-7	11-15	10	11-13	2	*tufA* *ctrA*	protein LipB *N. meningitidis* (3×10^{-26})
E138[1+]	315	1	6-7	11-15	10	11-13	2	*tufA* *ctrA*	protein LipB *N. meningitidis* (4×10^{-75})
B230[1]	356	1-3	6-7	1	10	11-13	2	ctrA	protein KpsC *E. coli* (3×10^{-51})
B323[1]	363	1	6-7	1	10	11-13	2	ctrA	protein CtrB *N. meningitidis* (2×10^{-64})
B322[2]	210		2	16-18	6	1	5	pilQ/λ740	HlyB *S. marcescens* (4×10^{-15})

B220[1]	341		2	16-18	6	≥18	5	pilQ/λ 740	
B108[1]	275		2	19-21	6	>18	5	pilQ/λ 740	
B132[1]	411	2	2	19-21	6	≥18	5	pilQ/λ 740	
B233[1]	164	1-3	2	19-21	6	≥18	5	pilQ/λ 740	
B328[1]	256	1-3	2	22-23	6	≥18	5	pilQ/λ 740	
E139[2]	324	2	2	19-21	6	≥18	5	pilQ/λ 740	
E145[2]	343	2	2	19-21	6	≥18	5	pilQ/λ 740	
B101[1]	254	≥20	2	19-21	6	≥18	5	pilQ/λ 740	
E103q	334		2	11-15	3-5	10	3	λ644	
B326[5]	314		2	11-15	3-4	10	3	λ644	
B326 (low reactivity)			5	6	16	2	1	*argF*	
B342	167		2	19	3-4	6-7	3	*iga*	
E136	249		2	7	1	3	3	*lepA*	

B208	177		1	2	3-4	2	1	*porA*	FeIII pyochelin receptor *P. aeruginosa* (5.10^{-4})
= B306[3#]	219	11	5	11-12	5	2	4	parC	
E114[3]	227	11	5	11-12	5	2	4	parC	
E115[3#]	251		5	11-15	5	2	4	parC	
E124[3]	208		5	11-12	5	2	4	parC	
E146[3]	146		5	11-15	5		4	parC	
E120[3]	263		5	3-4	5	16	4	opaB	
E107[3]	248	11	14-17	3-4	5	16	4	opaB	
E137[3]	274		14-17	3-4	5	16	4	opaB	Transposase Bacteriophage D3112 (6×10^{-12})
E142[3]	230		14-17	3-4	5	16	4	opaB	Protein Ner-Likc *H. influenzae* (6×10^{-23}) Protein binding to the DNA Ner, phage mu (3×10^{-18})
E116	379	5-7	11-13	3-4	2	6-7	8	λ375	
B313	436	9	9	3-4	13-14	5	2	λ611	
B341	201	8-10	9	3-4	13-14	5	2	λ611	
E102	238		11-13	3-4	19	5	2	λ601	Hypothetical protein H11730 *H. influenzae*

B134	428			multi ple					(7 x 10^{-74}) transposase I*SAS2* *Aeromonas* *salmonicida* (5 x 10^{-5})
B339	259			multi ple					transposase IS *1106* *N. meningitidis* (6 x 10^{-45})

The level of homologies found, as given by the Blastx program, are indicated in parentheses

*) The clones labelled with the index "1", "2" or "3" belong to regions "1", "2" or "3" respectively of the chromosome of *N. meningitidis Z2491*.

+) E109 and E138 are contiguous clones §) B306 and E115 overlap #) B236 also has a low reactivity in the region of *arg* F

q) Clone E103 contains a *Tsp509* I site and can therefore contain two inserts; however, since it reacts only with a single fragment *Cla*I (Oks) of the chromosome of *N. meningitidis* Z2491 and occupies only one position on the map, this clone is included here.

Firstly, it can be seen that the clones of region 1 all correspond to genes involved in biosynthesis of the capsule. These genes have previously been studied among the Nm of serogroup B (Frosch *et al.* 1989, Proc. Natl. Acad. Sci. USA 86, 1669-1673 and Frosch and Muller 1993, Mol. Microbiol. 8 483-493).

With the exception of a low homology with the haemolysin activator of *Serratia marcescens*, the clones of region 2 have no significant homology with published sequences, either in the DNA or the proteins.

Two of the clones of region 3 have interesting homologies with proteins which bind to the DNA, in particular the bacteriophage regulatory proteins and transposase proteins.

Clone B208 has a high homology with one of the conserved regions in one class of receptors (TonB-dependent ferric siderophor).

Clones B134 and B339 hybridize with several regions of the chromosome (at least 5 and at least 8 respectively).

Data relating to the sequences show that clone B339 corresponds to the Nm-specific insertion sequence S*1106*.

The translation of the clone B143 has a limited homology with the transposase of an *Aeromonas* insertion sequence (SAS2) (Gustafson *et al.* 1994, J. Mol. Biol. 237, 452-463). We were able to demonstrate by transfer on a membrane (Southern blots) that this clone is an Nm-specific entity present in multiple copies in the chromosomes of every meningococcus of the panel tested.

The other clones have no significant homology with the published neisserial sequences, and furthermore nor with any published sequence. These clones therefore constitute, with the majority of the other clones isolated, a bank of totally new Nm-specific loci.

Example 3: Study of region 2 of the Nm chromosome

. Determination and characterization of the sequence of region 2

PCR amplification is carried out with the chromosomal DNA of strain Z2491 of serogroup A, sub-group IV-1 using oligonucleotide primers formulated from each of the sequences of clones of region 2 in several different combinations. The PCR products which overlap are sequenced from the 2 strands using the chain termination technique and automatic sequencing (ABI 373 or 377).

To prolong the sequence beyond the limits of the clones available, partial SauIIIA fragments of 15 kb of the strain Z2491 are cloned in Lambda DASH-II (Stratagène).

The phages containing the inserts overlapping region 2 are identified by hybridization with clones of this region as probes. The DNA inserted is sequenced from the ends of the inserts, and these sequences are used to formulate new primers which will serve to amplify the chromosomal DNA directly, and not the phagic DNA.

An amplification of the chromosomal DNA is obtained using these new primers and those of the sequence previously available.

These PCR products are also sequenced from the 2 strands, which leads to a complete sequence of 15,620 bp (SEQ ID No. 36). The reading frames of this sequence which start with ATG or GTG and are characterized by a high codon usage index are analysed.

This analysis reveals 7 ORFs of this type which fill the major part of the sequence of 15,620 bp. The positions of these ORFs are the following:

ORF-1: 1330 to 2970 (SEQ ID No. 37); ORF-2: 3083 to 9025 (SEQ ID No. 38); ORF-3: 9044 to 9472 (SEQ ID No. 39); ORF-4: 10127 to 12118 (SEQ ID No. 40); ORF-5: 12118 to 12603 (SEQ ID No. 41); ORF-6: 12794 to 13063 (SEQ ID No. 43); ORF-7: 13297 to 14235 (SEQ ID No. 44); and ORF-8: 14241 to 15173 (SEQ ID No. 45).

ORF-4 starts with the codon GTG and overlaps a slightly smaller ORF (SEQ ID No. 41) in the same reading frame (9620-12118, frame 2), which starts with the codon ATG.

ORF-4 codes for a protein which has structural homologies with a family of polypeptides comprising pyocins (*Pseudomonas aeruginosa*), collcins and intimins (Escherichia coli), which are bactericidal toxins (pyocins, collcins) or surface proteins involved in adhesion of bacteria to eukaryotic proteins. ORF-7 encodes a protein, the sequence of which contains a potentially transmembrane region and which has structural homologies with periplasmic proteins or proteins inserted in the external membrane of bacteria. The structural homologies of ORF-4 and ORF-7 have been identified with the aid of the PropSearch program.

Investigation of sequences homologous to other ORFs in GenBank with the aid of the BLAST program revealed a homology between the N-terminal regions of ORF-2 and filamentous haemagglutinin B of *Bordetella pertussis* (43% similarity, 36% identical over 352 amino acids) and between ORF-1 and the protein fhaC of *Bordetella pertussis* (35% similarity, 27% identical over 401 amino acids). ORF-1 and ORF-2 are neighbouring genes in the strain Z249I and filamentous haemagglutinin B of *Bordetella pertussis* and fhaC are neighbouring genes in *Bordetella pertussis*, which reinforces the probability that these homologies reflect functional homologies.

. Confirmation of the specificity of region 2 with respect to Nm

Southern blots are carried out using the DNA probes obtained by PCR amplification of various parts of region 2 using oligonucleotide primers formulated from sequences of clones of region 2.

The approximate position of these oligonucleotides is shown on figure 4.

These are the oligonucleotides called R2001 (SEQ ID No. 46) and R2002 (SEQ ID No. 47) in one half of ORF-1, the oligonucleotides b332a (SEQ ID No. 48), e139a (SEQ ID No. 49), b132a (SEQ ID No. 50) and b233b (SEQ ID No. 51) in one half of ORF-1+the majority of ORF-2, and the oligonucleotides e145a (SEQ ID No. 52) and b101a (SEQ ID No. 53) in 1/3 of ORF-4+ORF-5 to 7.

The three Southerns are carried out under the following hybridization conditions:
16 h at 65ºC,
$NaPO_4$ 0.5 M, pH 7.2
EDTA-Na 0.001 M
1% sodium dodecylsulphate.

For the washing, heating is carried out for 10 min at 65ºC, and $NaPO_4$ 0.5 M, pH 7.2; EDTA-Na 0.001 M, 1% sodium dodecylsulphate are used.

Figures 5, 6 and 7 respectively show the Southern blots obtained with each of the abovementioned ORF parts.

The 14 tracks correspond respectively, in each of the Southerns, to
1: MS11 (Ng)
2: 403 (Ng)
3: FA1090 (Ng)

4: W1 (Ng)

5: 6493 (Ng)

6: marker (lambda hindIII)

7: Z2491 (Nm, gpA)

8: 7972 (Nm gpA)

9: 8013 (Nm, gpC)

10: 1121 (Nm, grouping not possible)

11: 1912 (Nm, gpB)

13: 32165 (Nc)

14: 8064 (Nl).

Given that a panel of strains of *Neisseria* is used in these experiments and that each well is charged with a similar amount of digested DNA, these 3 Southern blots clearly show that the sequences corresponding to region 2 are found in all the meningococci tested and that significant homologous sequences do not exist in the genome of the Ng of the strains tested.

Example 4: Identification of regions of the Nm genome absent from Nl and common with Ng

The technique described in example 1 is followed, but the chromosomal DNA of one strain of Nm (Z2491) and 2 strains of Nl (XN collections), equal parts of the DNAs of which are mixed, is used.

2 subtractions are performed using the R and J series of primers. Three different banks are thus obtained.

Two banks, called Bam and Eco, are obtained respectively by digestion of the chromosomal DNA of Nm Z2491 by *MboI* and *Tsp5091*; a third bank, called Cla, which results from digestion of the chromosomal DNA of Nm by *MspI*, is obtained

using the primer set RMsp10, RMsp24, JMsp10 and JMsp24. All the primers used are shown in the following table 2.

Table 2

Adapters for differential banks

Chromosomal DNA digested by		Cloning in pBluescript by
*Mbo*I	→	*Bam*HI
*Tsp*509I	→	*Eco*RI
*Msp*I	→	*Cla*I

First subtraction cycle

RBam12 : 3' AGTGGCTCCTAG 5' (SEQ ID No. 54)
RBam24 : 5' AGCACTCTCCAGCCTCTCACCGAG 3' (SEQ ID No. 55)

REcol2 : AGTGGCTCTTAA (SEQ ID No. 56)
RBam24 : 5' AGCACTCTCCAGCCTCTCACCGAG 3' (SEQ ID No. 55)
(REco 24 = RBam 24)
RMspl0 : AGTGGCTGGC (SEQ ID No. 57)
RMsp24 : 5' AGCACTCTCCAGCCTCTCACCGAC 3' (SEQ ID No. 58)

Second subtraction cycle

Jbaml2 : 3' GTACTTGCCTAG 5' (SEQ ID No. 59)
JBam24 : 5' ACCGACGTCGACTATCCATGAACG 3' (SEQ ID No. 60)

JEcol2 : GTACTTGCTTAA (SEQ ID No. 61)
JBam24 : 5' ACCGACGTCGACTATCCATGAACG 3' (SEQ ID No 60)

(JEco 24 = JBam 24)

JMspl0 : GTACTTGGGC (SEQ ID No. 62)
JMsp24 : 5' ACCGACGTCGACTATCCATGAACC 3' (SEQ ID No. 63)

After 2 subtractions, the entire product of each amplification is labelled and used as a probe.

The subtractive banks are checked by Southern blotting over a panel of 12 strains of *Neisseria* (chromosomal DNA cut by *ClaI*). The hybridization conditions are identical to those given in example 1.

These Southern blots are shown on figures 8A to 8C, which relate respectively to the *MboI/BamHI* bank, to the *MspI/ClaI* bank and to the *Tsp5091/EcoRI* bank.

The 12 tracks correspond respectively, to

1: Nm Z2491 (group A)

2: Nl 8064

3: Nm 8216 (group B)

4: Nl 9764

5: Nm 8013 (group C)

6: Ng MS11

7: Nm 1912 (group A)

8: Ng 4C1

9: Nm 1121 (grouping not possible)

10: Ng FA1090

11: Nc 32165

12: Nm 7972 (group A)

Examination of the Southern blots shows that the sequences contained in each bank are specific to Nm and are not found in Nl. Furthermore, the reactivity found with the strains of Ng suggests that some of these sequences are present in Ng.

Each of these banks was then cloned in pBluescript at the *BamHI* site for Bam, or the *EcoRI* sit for Eco, or the *ClaI* site for Cla. In order to confirm the specificity of the clones

with respect to the Nm genome, restriction of the individual clones and radiolabelling thereof were carried out. The clones showing reactivity for both Nm and Ng were kept for subsequent studies. These clones are shown on figures 9, 10 and 11, which give the profiles with respect ot Nm, Nl and Ng of 5 clones of the Bam bank (figure 9), 16 clones of the Eco bank (figure 10) and 13 clones of the Cla bank (figure 11).

These clones were sequenced using universal and reverse primers. They are

- Bam clones

partial B11 of 140 bp (SEQ ID No. 66), partial B13 estimated at 425 bp (SEQ ID No. 67), B26 of 181 bp (SEQ ID No. 68), B33 of 307 bp (SEQ ID No. 69), B40 of 243 bp (SEQ ID No. 70),

- Cla clones

C16 of 280 bp (SEQ ID No. 72), partial C20 estimated at 365 bp (SEQ ID No. 73), partial C24 estimated at 645 bp (SEQ ID No. 74), partial C29 estimated at 245 bp (SEQ ID No. 75), C34 of 381 bp (SEQ ID No. 76), C40 of 269 bp (SEQ ID No. 77), C42 of 203 bp (SEQ ID No. 78), p C43 of 229 bp (SEQ ID No. 79), C45 of 206 bp (SEQ ID No. 80), C47 of 224 bp (SEQ ID No. 81), C62 of 212 bp (SEQ ID No. 82), and C130 (5'...) estimated at 900 bp (SEQ ID No. 83), and

- Eco clones

E2 of 308 bp (SEQ ID No. 84), partial E5 estimated at 170 bp (SEQ ID No. 85), partial E22 estimated at 300 bp (SEQ ID No. 86), E23 of 273 bp (SEQ ID No. 87), E24 of 271 bp (SEQ ID No. 88), E29 of 268 bp (SEQ ID No. 89), partial E33 estimated at 275 bp (SEQ ID No. 90), partial E34 estimated at 365 bp (SEQ ID No. 91), E45 of 260 bp (SEQ ID No. 92), E59 estimated at greater than 380 bp (SEQ ID No. 93), E78 of 308 bp (SEQ ID No. 94), E85 of 286 bp (SEQ ID No. 95), E87 of 238 bp (SEQ ID No. 96), partial E94 greater than 320 bp (SEQ ID No. 97), partial

E103 greater than 320 bp (SEQ ID No. 98) and E110 of 217 bp (SEQ ID No. 99).

Mapping of each clone was carried out on the chromosome of Nm Z2491 as described in example 1. The results obtained are given on the right-hand part of figure 2. It is found that these clones correspond to regions called 4 and 5. These regions are therefore made up of sequences present both in Nm and in Ng, but not found in Nl. It is therefore regarded that these are sequences which code for virulence factors responsible for the initial colonization and penetration of the mucosa. Region 4 is located between *argF* and *regF* on the chromosome of Nm 2491 [sic], and region 5 is located between the lambda 375 marker and *penA*. This region probably contains sequences which code for an Opa variant and a protein which binds transferrin.

A comparison with the known sequences in the databanks has half [sic] that in region 4 only the clone C130 has a homology, that is to say with *MspI* methylase. In region 5, no homology with known sequences was found with the clones C8, E2, B40, C45, E23 and E103. For the other clones, the homologies are the following:

B11 arginine decarboxylase SpeA; C29 arginine decarboxylase SpeA; C62 oxoglutarate/malate transporter; repetitive DNA element; E34 repetitive DNA element; E94 murine endopeptidase MepA ; C47 citrate synthase PrpC; E78 citrate synthase PrpC

Example 5: Demonstration of the presence of one or more strains of *Neisseria meningitidis* in a biological sample

A biological sample of the cephalorachidian fluid, urine, blood or saliva type is taken.

After filtration and extraction, the DNAs present in this

sample are subjected to gel electrophoresis and transferred to a membrane by Southern blotting.

A nucleotide probe constructed by labelling SEQ ID No. 5 with ^{32}P is incubated with this transfer membrane.

After autoradiography, the presence of reactive band(s) allows diagnosis of the presence of *Neisseria meningitidis* in the sample.

Example 6: Vaccine composition including in its spectrum antimeningococcal prophylaxis and intended for prevention of any form of infection by Neisseria meningitidis.

The peptide coded by a sequence including SEQ ID No. 10 is conjugated with a toxin.

This conjugated peptide is then added to a composition comprising the anti-*Haemophilus* and antipneumococcal vaccine, or any other childhood vaccine.

After having been sterilized, the resulting composition can be injected parenterally, subcutaneously or intramuscularly.

This same composition can also be sprayed on to mucosa with the aid of a spray.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: I.N.S.E.R.M

(B) STREET: 101, rue de Tolbiac

(C) CITY: PARIS CEDEX 13

(E) COUNTRY: FRANCE

(F) POSTAL CODE (ZIP): 75654

(ii) TITLE OF THE INVENTION: DNA, specific proteins and peptides of the Neisseria meningitidis species bacteria, methods for obtaining them and their biological applications.

(iii) NUMBER OF SEQUENCES: 99

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (OEB)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 257 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GATCCGCTGC CGGCAGACGA ATATCAAGAC ATCTTCGATT TTATGAAACA GTATGACTTG 60

TCTTACCCGT ATGAATATCT GCAGGATTGG ATAGATTACT ATACGTTCAA AACCGATAAG 120

CTGGTATTTG GTAACGCGAA GCGAGAGTGA GCCGTAAAAC TCTGAGCTCC TGTTTTATAG 180

ATTACAACTT TAGGCCGTCT TAAAGCTGAA AGATTTTCGA AAGCTATAAA TTGAAGCCCT 240

TCCACAGTAC ATAGATC 257

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 276 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

GATCATGTTC AAATAGATAG GCATGGGAAG CTGCAGCTCT AACGTCCATG AAAATATGTT 60

GCATAGCTGC AAGCGGAACG CCTTTTCTTT CATCTACATA ATCTATAGAG TCAAGGCAAC 120

CGCTATTGAA ATTAGCAGTA TTGCCTATGA TTACATTAGT AATATGCTCA TACCATTTTT 180

GGGTGGTCAT CATATTGTGC CCCATTGTTA TCTCCTTATA TTGGTTTTAG AAGGAACTTT 240

GACAGGAAGA ATAACGGCCT TACCTGTTTG ACGATC 276

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 428 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GATCTGGTGG TGTTTGCACA GGTAGGCGCA TACTTGTTCG GGACTGAGTT TGCGGCGGAT 60

AAGGGTGTCG ATGTGCTGAA TCAGCTGCGA ATCGAGCTTA TAGGGTTGTC GCTTACGCTG 120

TTTGATAGTC CGGCTTTGCC GCTGGGCTTT TTCGGCGCTG TATTGCTGCC CTTGGGTGCG 180

GTGCCGTCTG ATTTCGCGGC TGATGGTGCT TTTGTGGCGG TTAAGCTGTT TGGCGATTTC 240

GGTGACGGTG CAGTGGCGGG ACAGGTATTG GATGTGGTAT CGTTCGCCTT GGGTCAGTTG 300

CGTGTAGCTC ATGGCAATCT TTCTTGCAGG AAAGGCCGTA TGCTACCGCA TACTGGCCTT 360

TTTCTGTTAG GGAAAGTTGC ACTTCAAATG CGAATCCGCC GACCTCTTTC AGTTACAGCA 420

GCTTGATC 428

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 390 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GATCCTGCAT TGACATCGGC CTTGGCTGTC AGGGTATTGT GACCGGTAAA GTCGGCATTA 60

CCGTTGGCCA ATAAGGATAC ATGACCGTCT GCAGAAACAG CATGAAGGCC GTCTGAAACG 120

ATATTGCCCT GCAATGCGGT GGTTTCGAGA GCCTTGGCTG CGTTCAGCTT GGTATTGCGA 180

AGCTGAATAT TGCCTTTGGC TGCCTGAATG TGCAGATTAC CCGAGTTGGT ACGCAGATTG 240

GTATTGGTAA CATTCAGCAA GCCTGCCTCC ACACCCATGT CTTTTGAGGC AGTGAGGGTT 300

TTACTGGTGC CGGTAATATG GGCAGCGTTA TCCGATTTCA AATGGATGCT GGCCGGCAGA 360

CAAATCTTTA TCAACATTCA AATTCAGATC 390

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 177 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GATCAGATTG GTGAAGACGG TATTACCGTC AATGTTGCAG GCCGTTCGGG ATATACGGCG 60

AAAATCGACG TGTCTCCGAG TACCGATTTG GCGGTTTATG GCCATATTGA AGTTGTACGG 120

GGTGCAACGG GGTTGACCCA ATCCAATTCA GAGCCGGGTG GAACCGTCAA TTTGATC 177

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 341 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

GATCAATGAT GCTACTATTC AAGCGGGCAG TTCCGTGTAC AGCTCCACCA AAGGCGATAC 60

TGAATTGGGT GAAAATACCC GTATTATTGC TGAAAACGTA ACCGTATTAT CTAACGGTAG 120

TATTGGCAGT GCTGCTGTAA TTGAGGCTAA AGACACTGCA CACATTGAAT CGGGCAAACC 180

GCTTTCTTTA GAAACCTCGA CCGTTGCCTC CAACATCCGT TTGAACAACG GTAACATTAA 240

AGGCGGAAAG CAGCTTGCTT TACTGGCAGA CGATAACATT ACTGCCAAAA CTACCAATCT 300

GAATACTCCC GGCAATCTGT ATGTTCATAC AGGTAAAGAT C 341

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 164 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GATCCAACTG TTTGATTTTA CTGGCTGCTT CTCCATGCGC GGTATTGACC AAAGCCGCAA 60

GGATATTCGC TTCCAGATTG TCTTTCAGGC TGCCGCCGTT GACAGCGGTA TTAATCAGTG 20

CGGCACTGCC CGCATTGGCT AGGTTGACGG TCAGGTTGTT GATC 164

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 219 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GATCAATCAC ACATCTTGTC ATTTTTTCGA TTCCTTCATT TCGGTTTCTA ATGTTTCAAT 60

TCTTGCGGCC ATTTCCTGAA TGGCTTTAGT CAAAACGGGG ATGAACGCTT CGTATTCGAC 120

GGTGTAGGTA TCGTTTGTTT TATTTACCAT CGGCAATCGA CCATATTCAT CTTCCAGCGC 180

AGCAATGTCC TGGGCAATAA ACCAATGCCG CAACCGATC 219

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 356 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GATCTTGGGT AAGCCCCCAA CCTGCATAGA AAGGCAGGCC GTAGCAGCTG ACTTTTTTGC 60

CGCGCAACAA GGCTTCAAAA CCGGTCAGCG AAGTCATGGT ATGTATTTCG TCTGCGTATT 120

GGAGACAGGT CAGGATGTCG GCTTGTTCGG CGGTTTGGTC GGCATATCGT GCAGCATCAT 180

CAGGGGAAAT ATGGCCGATG CGGTTACCGC TGACTACATC GGGATGCGGT TTGTAGATGA 240

TATAGGCATT GGGGTTTCGT TCGCGTACGG TACGGAGCAA ATCCAGATTG CGGTAGATTT 300

GGGGCGAACC GTAGCGGATA GACGCATCAT CTTCAACCTG GCCGGGAACG AGGATC 356

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 210 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GATCCGCTTT CAGTTTCCGT ACCGGTGGCA TCAGTCAAGT CCGTTTTGTG CACCAAACCG 60

CGTCCATATG AAACATAAAA CAAATCGCTT AAGCCCAAAG GGTTATCGAA CGATAAAGCG 120

ACATTTCCTT GATATTTGCC GGTCGTTTTG CCGCCCGCAT CATCTATACC GATACTGAAC 180

CGTATGGGTT TATTCTGCTG CCATTTGATC 210

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GATCCCGAAA CGCAATTGGT CGAAAGCTAT ATGCTGAACG ATGTGTTGCG GTTTTGGGAC 60

AGCGCAGGTT TGGGCGATGG GAAAGAAGCC GACCGCGCCC ATCGGCAAAA ACTGATTGAT 120

GTCCTGTCTA AAACCTATAC TCATTCGGAT GGGCAGTGGG GCTGGATAGA TTTGGTGTTC 180

GTTATCCTTG ACGGCAGCTC CCGCGATTTG GGTACGGCCT ATGATTTGTT GAGGGATGTT 240

ATCCTTAAAA TGATTGATC 259

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
A LENGTH: 436 base pairs
B TYPE: nucleotide
C STRANDEDNESS: single
D TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GATCAAATGG ATGATTTATA TAGAATTTTC TTTTACGACT GCGTGCCGTT TGAAAAGAAA 60

ATGCACAATC CCGTATCTCA TCGTGCCATA GATTTTTCAA AGACTCCGGA AGCCATATTT 120

CGTTGCAATC TGCATACCGA ATTGAAGAAG AAGCGTAAAT TAGCGTTACG TTTAGGCAAG 180

CTGTCGGACA ATACAGCATG GATATTAAAA CCCCAAGTCA TGAAAAATCT TCTGAAAAAC 240

CCGTCAACTC AAATTACGGA AAACGATGTC GTGCTCGATG TTAAACAAAA AGGTGTAGAT 300

ATGCGTATAG GCTTGGATAT TTCATCTATT ACCTTAAAAA AACAAGCCGA TAAAATCATC 360

TTGTTTTCTG GTGATTCCGA TTTTGTCCCA GCAGCCAAAT TAGCCAGACG GGAAGGTATC 420

GATTTTATTC TTGATC 436

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 363 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GATCGTTTTA CGTCGCAATC GAGCTTTGTG GTGCGCTCGC CTAAAAGCCA ATCTTCTCTC 60

AATGGCCTGG GTGCCATTTT GCAGGGCACA GGTTTTGCCC GTGCGCAAGA CGATATTTAT 120

ACCGTGCAGG AATATATGCA GTCGCGTTCG GCTTTGGATG CGTTGCGTAA GAAAATGCCC 180

ATTCGCGATT TTTATGAAAA AGAAGGCGAT ATTTTCAGCC GTTTTAATGG TTTTGGCCTG 240

CGTGGCGAGG ATGAGGCGTT TTATCAATAC TACCGTGATA AGGTATCCAT CCATTTTGAC 300

TCTGTCTCAG GCATTTCCAA TTTGAGCGTT ACATCGTTTA ATGCCGGTGA ATCTCAAAAG 360

ATC 363

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 314 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GATCTTGCGT CATTTATATC TTCACCGATA TTGCAATTAC CGCCGTTCCA GTTGAAATAA 60

CAACGACTAA AATTGTAGTT CCTAAAAGAA TCATTCCTAT TCTTGCGTAC CATTTCCCAA 120

TAATTGCGCC CGACAATTTC CATTTAATGC TCCATCAGTT CTTTTACTTC CGGAAATCTG 180

CTGTAATCTG ACATAAGACG CATAATTGAA CTATCAACGC CGTAACAGCC ATAGGTTTTA 240

ATACCGTTTT CGGCGTGTTC CCAAATGCAA TTACTGTATT CGTAGCCTTT TACAAATTTA 300

TCGGTTTCGG GATC 314

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 256 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GATCATACGA ATCTACCCTA AAATACCCCG TCGCCGATTT AGGATTGGCT ACATAAAGCT 60

CATTATAAGG GTATTTTGAT GACATGATAC GGTTAAATTC ATTGCCGTTG TTTATCCTGA 120

TTCTATAAAT TGGTTCAACA GCAAAGCCTC TGGATTCCCT TAATTGATTA TAATATTGCC 180

TGTATGTTTG TACATCATGT CTTGTCCACG GCTCTCCAGG AGTCCTCAGA ATAGCAATCC 240

CGTTAAATTT CGGATC 256

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 235 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GATCCACGCC TGTGCCTACC TTGGCTTTTT GTTCGCCAAA CAAGGCATTT AAGGTTGAGG 60

ACTTGCCGAC ACCTGTCGCA CCGACAAGCA AGACATCCAA ATGACGGAAA CCGGCTGCTG 120

TGACTTTTTG CCCGATTTCA GAAATACGGT AACGATGCAT ATGCGCTCCT ACCAGCCAAA 180

AAAAGAAGCA ACCGTGCTAA TCGCCCCTCC AATCGCTTTT GCAGCACCGC CGATC 235

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

GATCCAACGG GCATCGCTGT CCTTACTCGG TGTGGTTTGA CCGCTGATTT GTCCTTCTTC 60

GTCAACTTCT ATGGCCTGAC GCTGTTTGCT GCCGGCGGTC TGGATAATGG TGGCATCAAC 120

GACGGCGGCG GATGCTTTCT CTATTTTTAG GCCTTTTTCG GTCAGTTGGC AGTTAATCAG 180

TTTGAGTAAT TCGGACAGGG TGTCGTCTTG CGCCAGCCAG TTGCGGTAGC GGCATAAGGT 240

ACTGTAATCG GGGATGATC 259

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 201 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GATCTGTGCC GTTGATTTTA TCTTTCAGAT GCAGCATCGA ATATCGGAAA GCCAAATCAG 60

CAATTCTTTT TGCATCGTGT GGATTTTGAG ACGGGCCTAA TGACCGTACC CGCTTAATAA 120

AAAATGCACC GTCAATCAAA ATGGCGGTTT TCATATTGCT TCCCCTATAT TTGTCAAAGA 180

TATAAAAAAG CCCTTGGGAT C 201

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 334 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

AATTCAAAGG AGGCATTTGT TGCAAGAAAA GTACAAAGTG ATTTGCAAAA AGCATTGAAT 60

GCTAGCAACT ATAACAAGCA GCAATATGCA AGACGTGCGG CAACAGCGTT AGAGAATGCT 120

TCAAAATCAA AAGTTATGGC AGCGAATTCT TTTTGATCTA TCTTGTGCGA ACGGGTCAAA 180

TATTCTTCGT ACATTGAGTT AATCGTACCA ATCGCCCTAA CCACATTTTC ATCAGAAAAT 240

ATGGAAATAA TAGCATCCCT ATACGCACCT AGTGTAATAT TGTTTCTATT ATTAGTTATA 300

GCATTATTCG AATACATAAT AGCACCTCCA AATT 334

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 238 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AATTCCTGCG CACCTTTGCC GATGGGGAGA TAATCGCCTT TTTGCAGCAT TCTGCCCTGA 60

TGGCCGCCGA AACCGGCTTT CAGGTCGGTA CTTCTCGAAC CCATCACTTC CGGCACATCA 120

AATCCGCCCG CCACGCACAC ATAGCCGTAC ATGCCCTGCA CGGCACGCAC CAGTTTCAAG 180

GTCTGCCCTT TGCGGGCGGT ATAACGCCAA TACGAATAGA CCGGTTCGCC GTCCAATT 238

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 249 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

AATTGGGCGA GATGCTGCCG GAAACGGATT TAAAACAGAT TGCGGCGGCA GTGTTGAAGA 60

CGAACGATGA GGCGGCATTG CAGAAGGTGG TGAAAACGGC CAAAGGCAAT GCGCGGAAAC 120

TGTCGAAGCT GCTGCTGATT GTGGACTATT TGTTGCAGGT TAACCCTGAT GTTGATTTGG 180

ATGATGATGT AATCGAACAC GCGGAAACCT ATTTAATCCA CTAAACCTTT GACAGATAAG 240

GCAATTAATT 249

2. INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 212 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

AATTTATGTA CGGTTTTGCC GTTTGCAGTC AGCCAGTCGG CAAGGCGCAG AAAAAAATCG 60

CCGACAGGGC CTTGAAGCAG CAGGATATTT TCTGCGCTTT CAAGCAGGTT TTGCAGGTTA 120

TTTTTGAGGA CGGTCTGTTT CATGTTGCAA TGTGGTTTTG TTTTTTATGT AATAGTTTTA 180

GGTTGAACTT TCAAGCATAC GCCAAGAGAA TT 212

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 227 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

AATTCAGTGC CTGCGTCATA TCACGGCTAC CTTGTGGTTC AGGGTTACTG TATCGCCCGC 60

GGCATCGACG GCTTCAATAT GCAGCTTCAG CCAGCCGTGC TGCGGGGCGG ATGCGGTTAC 120

TTGGATGGAT TGGGCGCGTT TGGACTGAAT CACGGGCTGC AAGGCTTGCT CGGCGTACTG 180

TTTGGCCAGT ACTTCGATGC GCTTTAAATG CTTTTGGCGG CGCAATT 227

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 167 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GATCCAGGAC TCAAAAACCG ATTTCCTAAT AGAGTGTCTA ATATCCCAAT CTTTTTTACC 60

CCCTCTGCTG TAGAATTGAT AGAGAAAGTT TGTCTATCTT TTTCATATAC CCATGCCTTC 120

TTTTTATCAT TGTAGCTAAC ATAACCGCCA AACAATGCTT CTAGATC 167

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 251 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

AATTCTTGCG GCCATTTCCT GAATGGCTTT AGTCAAAACG GGGATGAACG TTTCGTATTC 60

GACGGTGTAG GTATCGTTTG TTTTATTTAC CATCGGCAAT CGACCATATT CATCTTCCAG 120

CGCAGCAATG TCCTGGGCAA TAAACCAATG CCGCAACCGA TCTTCTTTAT GACTGCCGTC 180

CTTGATTGGA TTCGCCCACC ATTCGCGGAC TTTGTCCGCT CGTTCATCTG CCGGCAAGTC 240

TTTGAATAAT T 251

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 207 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

AATTCCCGAC TATCGCGGAT GCGTAGTTTT TGCCGGTGGG CAAGAGCAGG TGTGGGATAA 60

GTTAGGTGAT TTGCCCGATG GCGTCAGCCT GACCCCGCCT GAATCGGTAA ATATTGACGG 120

CTTAAAATCC GTAAAACTCG TCGCATTAAA TGCTGCCGCT CAGGCTTTTA TTAACAAGCA 180

CGCCGGTATC GACAGCGTAC CTGAATT 207

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 379 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:

(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

AATTGTTTGG GAATAATCCA AACAAACAGC ATCAGGATAG CGGCGGCGGT CAGGCTGCCT 60

GAAAGGATTT TGCCGGGGTT TTTTGTAGGC AAAGCGGACG AGAAACCAAA GCAACAGCAG 120

CATGGTGTCC CAATAGCCGA TTGAGAATAG GATGGCCAAA CCTTCTAGGA AATGGCGTAA 180

ATCGTTTGTG GTAACCATGG GTAGTTCCTG TGGTTAAATG TGCAGGCTGC TTTTTGCCGA 240

ACCTTGCCGC ATCTCAAAAG CAGCCTGCGC TTCAGCGTTG CGTTACGCAG TAAAATAATG 300

AATATTTGTA ACGGCTTGGG TATTTTTTGT CAATATTCCC GCCCTTCCCT TAACAGCTGC 360

CGCGCTTTCC GTTAAAATT 379

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 274 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

AATTCGCCGA AATCAGGCTG CTGCTCGATA ATCGGCGCGG CCGATTGGCG TTGTGCCTCG 60

ATTAAATCCA TCTTGTCTTG CAGACGTTTG GCCTGGCCTT TGCGGCGGCG TTCGGCCAGT 120

TGTTCCATCC GCGTTTCCGC AAATGCCGCC CGTTTGTTGC CGTTGAATAC CGCTTTGCAA 180

ATCACCTTGC CCTGCATATC CTTCACAATC ACATGGTCGG CATCGTGGAT GTCGTAAGCC 240

ACCCGTACCT TCTGACCGCT GTAATCCAGC AATT 274

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 263 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

AATTCCGTTC TTATTGGGCT TTTTCCATCC ATCGGGTATG CCTGAAGGGA ACGCAAACCC 60

TGCCACTTGC CCATCGCTCC ATTCCCGCAT TAGCGCGTCT GACGGCAAGT GTTCTCGCGC 120

CCAATCAAGC CACGCCTGCC GCATTGCGGC CTTGTCCTGC TGAAAACTTC GCAGTGCTTT 180

TGCAACCGGC CCATCATTAA CTTCAATCAA ATAAATCATT ATATTTGCGT TCATTTTTCC 240

TACACCTTCG CCACATCCAA ATT 263

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 316 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis

(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

AATTGTTCAA GAAAAAAGTC GGCACGGCGC GGCAACGGGG AAAATGCGTT GACGCCGTCT 60

TTTTCTAAGG TGATGTAGTA GGGGCGGAAA TAGCCTTCTT CAAACGCCCA GAAACTGGCT 120

TGGTTTTCGT TTGCAATGCG TTTTGCAATG ACGTGATAAG GGCGTGTGTC GCCAAAGCAG 180

ACAACGGCCT GGATGTGATG TTGAGTGATG TATTCTTGCA AAAACTCAGG AAAGGCGTCG 240

TAGTTGTCGT TAAAAACAAC GGTATGCGCT TGAGTGGGCG GATAAAAATA GTCGTCGCCT 300

GCATTAAAGT TGAATT 316

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 324 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

AATTCAATCA ACGGAAAACA CATCAGCATC AAAAACAACG GTGGTAATGC CGACTTAAAA 60

AACCTTAACG TCCATGCCAA AAGCGGGGCA TTGAACATTC ATTCCGACCG GGCATTGAGC 120

ATAGAAAATA CCAAGCTGGA GTCTACCCAT AATACGCATC TTAATGCACA ACACGAGCGG 180

GTAACGCTCA ACCAAGTAGA TGCCTACGCA CACCGTCATC TAAGCATTAC CGGCAGCCAG 240

ATTTGGCAAA ACGACAAACT GCCTTCTGCC AACAAGCTGG TGGCTAACGG TGTATTGGCA 300

CTCAATGCGC GCTATTCCCA AATT 324

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 230 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

AATTATGCAA AAAAACGCAA CGCCGAAAAA CTGGCACCGC GCGGATATTG TTGCTGCTTT 60

GAAAAAGAAA GGCTGGTCAC TTCGAGCACT TTCAATAGAA GCGGGGTTGT CGCCGAATAC 120

GCTTAGAAGC GCACTGGCCG CCCCTTATCT TAAGGGAGAA AGGATTATTG CCGCTGCAAT 180

CGGAGTGGAA CCGGAAGAGA TTTGGTCCGA ACGGTATGCA GATCGGAATT 230

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 249 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

AATTTAATCG GTGGAATGCC TGTTCAACCG CACCAATCCC GCTGAATACG GTTGCTAATC 60

TAATATGTGA ATCAGGTTTA AGAAAAGTTT TAGATTTCCA ACCTTGTTGA CTGGGAAAGA 120

GCAAAGTTTT TTGTAATCGA GTATCGTGTG TCTGTGCCAT TGTCGAAATA GTCATACTTA 180

TATCGTTCTG TTTATCTTAT CAATATGAAA ACTACATCGT TGATTGCCCT GACAATGCCT 240

TGGTCAATT 249

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 343 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

AATTCTTGTC CCGGAGTCCA ACGTATATTT ACCCTCCTGC GAGCTAAAAG ACTATTATTC 60

TCCACTGCCA CAGTAGCCGC ATTCACCGCC GTATTCACAT CCCCTTTAAC CAATGCCACT 120

GCGCTGCCTG CGATAATCTG CGAGTAGGCT ATGACTTTTT GGCGTTCTTG GGGTGACAGT 180

TTGCCTACAT CGCGTCCGTC CAACAGGGTT TCTCCCACCA TCTCGCCGAC TGCCGCGCCG 240

ATTGCGCCGT CCCGACATTT GCCTTTATTT GCTACCGCCG ATGCACAGCC TGCTACGGCA 300

TGGGCTATCT TGTGGGCAAT GTAGTCTTCG CTGAGATTAA ATT 343

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 184 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGIN:
(A) ORGANISM: Neisseria meningitidis
(B) STRAIN: Z2491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

AATTCTTCAA ACATCGTTTC GATAATCGGG TCGGTGTACA CACTGATGCG GTCGCCCGCA 60

CGGCTTTGAC CGGCTCGGAA AATATAGGCG GTGGCTTTGC CGTCGGCGAT GTCGACGCAC 120

CAACGCCAGA TGGCGTCTTC GGTATTCAAA CAATCACCCG CACAGCTTTC ACCTGCGCGG 180

AATT 184

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

TATGCTCAAT CTCATTTTCA AAATGCAAAA CTTTTCTGAT TTTTCCTACT TTTTGCTCAA 60

TATTAGGAAG GTTTTAGGCA ATTGAAAATT TTTTGGCGCA TTTTTATGCG TCAAATTTCG 120

TTAACAGACT ATTTTTGCAA AGGTCTCCGT CTGTAAAAGC AAGGATAGGG CATCTGCCCT 180

TTTGATTGTT TGATTAACGA TACAAGGAGT TTCAAAATGA GAGTTTTATA GTGGATTAAC 240

AAAAACCAGT ACAGCGTTGC CTCGCCTTGC CGTACTATTT GTACTGTCTG CGGCTTCGTC 300

GCCTTGTCCT GATTTAAATT TAATCCACTA TATGTGTTCA TGAAATGACT TGGGTCGGAG 360

GCTCAGGTAA TGCGCAACAA AGTTCATATT ATTGCGAAAT TTGCGAATCT GCAGGGCTTA 420

ACGATACGGG AAATCCTGAT AAATCTTTAG GATTGCCAAA CAATACGTTC AGTAATCCGC 480

CTGGTTGGGG AGCTACAATC GGAGCTTTAG CAGGTAGCCG CATAGGTATG CCTGAATTTG 540

GTACGTTTGC GAGCCATGCC ATTGAAAATT TCGACTGGTC ATGGTATCGA CGTTATAGGG 600

AAATTGCCGA AACGATTGAA CGAGAATATT CAGGCGGTTT GCCTTAATAG TTGAGGAGGT 660

CATGATGTTT GCCAAACATT ATCAATTCAT CGCACTCGGC ATCATGCTGC TTCTTTATAT 720

GTTGATTCTC TATACGACCG ATTTTTCCAA TCTGACGTAT TGGATGCTGT TTTTTATCTG 780

TTTTATTACA GGAAAAATAT TAGCTCGTTT GTTAGAGAAA AGCTTTAAAT AAAATAGCAG 840

CTAGTCGCAA AAGGTCGTCT GAAACCTTTT CAGGCGGCCT TTCTAAAATA CATCCAACTT 900

CCTAATCCCT ATTTTTCAAA AAGGAAATCT ATGCCCCATC TGCAAAACCT GTCTTTGGGC 960

TTAAAGAAAA AGCTGCCTGT TATCCTGCAA ACAGAAATAT CAGAATGCGG CTTGGCATGT 1020

CTGGCGGCTG TGGCGGGATT TCATGGTTTC CATACGAATT TACGCGCACT GCGTTCAAAA 1080

TACTGTCCGA GACCTTTGCA AAATTCCCCA AAATCCCCTA AATGTCTTGG TGGGAATTTT 1140

GGGGAATTTT GCAAAGGTCT CATTCTATAA CTGTAAATAC TTTTAAATTT ATGACAAAAT 1200

AGTAAATATT GCTAAAATAA TATTGATGTC ATGAAATTTT TTCCTGCTCC ATGTCTGTTG 1260

GTTATCCTGG CTGTCATACC CCTTAAAACC TTAGCTGCCG ATGAAAACGA TGCAGAACTT 1320

ATCCGTTCCA TGCAGCGTCA GCAGCACATA GATGCTGAAT TGTTAACTGA TGCAAATGTC 1380

CGTTTCGAGC AACCATTGGA GAAGAACAAT TATGTCCTGA GTGAAGATGA AACACCGTGT 1440

ACTCGGGTAA ATTACATTAG TTTAGATGAT AAGACGGCGC GCAAATTTTC TTTTCTTCCT 1500

TCTGTGCTCA TGAAAGAAAC AGCTTTTAAA ACTGGGATGT GTTTAGGTTC CAATAATTTG 1560

AGCAGGCTAC AAAAAGCCGC GCAACAGATA CTGATTGTGC GTGGCTACCT CACTTCCCAA 1620

GCTATTATCC AACCACAGAA TATGGATTCG GGAATTCTGA AATTACGGGT ATCAGCAGGC 1680

GAAATAGGGG ATATCCGCTA TGAAGAAAAA CGGGATGGGA AGTCTGCCGA GGGCAGTATT 1740

AGTGCATTCA ATAACAAATT TCCCTTATAT AGGAACAAAA TTCTCAATCT TCGCGATGTA 1800

GAGCAGGGCT TGGAAAACCT GCGTCGTTTG CCGAGTGTTA AAACAGATAT TCAGATTATA 1860

CCGTCCGAAG AAGAAGGCAA AAGCGATTTA CAGATCAAAT GGCAGCAGAA TAAACCCATA 1920

CGGTTCAGTA TCGGTATAGA TGATGCGGGC GGCAAAACGA CCGGCAAATA TCAAGGAAAT 1980

GTCGCTTTAT CGTTCGATAA CCCTTTGGGC TTAAGCGATT TGTTTTATGT TTCATATGGA 2040

CGCGGTTTGG TGCACAAAAC GGACTTGACT GATGCCACCG GTACGGAAAC TGAAAGCGGA 2100

TCCAGAAGTT ACAGCGTGCA TTATTCGGTG CCCGTAAAAA AATGGCTGTT TTCTTTTAAT 2160

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GGCAAACAAT ATCAGAGCAG CCTGGCCGCC GAGCGCATGC TTTGGCGTAA CAGGTTTCAT 2280

AAAACTTCAG TCGGAATGAA ATTATGGACA CGCCAAACCT ATAAATACAT CGACGATGCC 2340

GAAATCGAAG TGCAACGCCG CCGCTCTGCA GGCTGGGAAG CCGAATTGCG CCACCGTGCT 2400

TACCTCAACC GTTGGCAGCT TGACGGCAAG TTGTCTTACA AACGCGGGAC CGGCATGCGC 2460

CAAAGTATGC CCGCACCTGA AGAAAACGGC GGCGGTACTA TTCCAGGCAC ATCCCGTATG 2520

AAAATCATAA CCGCCGGATT GGATGCAGCG GCCCCGTTTA TGTTGGGCAA ACAGCAGTTT 2580

TTCTACGCAA CCGCCATTCA AGCTCAATGG AACAAAACGC CTTTGGTTGC CCAAGACAAG 2640

TTGTCTATCG GCAGCCGCTA CACCGTTCGC GGATTTGATG GGGAGCAGAG TCTTTTCGGA 2700

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ATTTAGCCTG TTGGCCGCTT TCAACAGGTT CAAACACATC GCCTTCAGGT GGCTTTGCGC 15600

ACTCACTTTG TCATTTCCAA 15620

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 580 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Protein
(B) LOCATION: 1..580

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Met Lys Phe Phe Pro Ala Pro Cys Leu Leu Val Ile Leu Ala Val Ile
1 5 10 15

Pro Leu Lys Thr Leu Ala Ala Asp Glu Asn Asp Ala Glu Leu Ile Arg
20 25 30

Ser Met Gln Arg Gln Gln His Ile Asp Ala Glu Leu Leu Thr Asp Ala
35 40 45

Asn Val Arg Phe Glu Gln Pro Leu Glu Lys Asn Asn Tyr Val Leu Ser
50 55 60

Glu Asp Glu Thr Pro Cys Thr Arg Val Asn Tyr Ile Ser Leu Asp Asp
65 70 75 80

Lys Thr Ala Arg Lys Phe Ser Phe Leu Pro Ser Val Leu Met Lys Glu
85 90 95

Thr Ala Phe Lys Thr Gly Met Cys Leu Gly Ser Asn Asn Leu Ser Arg
100 105 110

Leu Gln Lys Ala Ala Gln Gln Ile Leu Ile Val Arg Gly Tyr Leu Thr
115 120 125

Ser Gln Ala Ile Ile Gln Pro Gln Asn Met Asp Ser Gly Ile Leu Lys
130 135 140

Leu Arg Val Ser Ala Gly Glu Ile Gly Asp Ile Arg Tyr Glu Glu Lys
145 150 155 160

Arg Asp Gly Lys Ser Ala Glu Gly Ser Ile Ser Ala Phe Asn Asn Lys
165 170 175

Phe Pro Leu Tyr Arg Asn Lys Ile Leu Asn Leu Arg Asp Val Glu Gln
180 185 190

Gly Leu Glu Asn Leu Arg Arg Leu Pro Ser Val Lys Thr Asp Ile Gln
195 200 205

Ile Ile Pro Ser Glu Glu Glu Gly Lys Ser Asp Leu Gln Ile Lys Trp
210 215 220

Gln Gln Asn Lys Pro Ile Arg Phe Ser Ile Gly Ile Asp Asp Ala Gly
225 230 235 240

Gly Lys Thr Thr Gly Lys Tyr Gln Gly Asn Val Ala Leu Ser Phe Asp
245 250 255

Asn Pro Leu Gly Leu Ser Asp Leu Phe Tyr Val Ser Tyr Gly Arg Gly
260 265 270

Leu Val His Lys Thr Asp Leu Thr Asp Ala Thr Gly Thr Glu Thr Glu
275 280 285

Ser Gly Ser Arg Ser Tyr Ser Val His Tyr Ser Val Pro Val Lys Lys
290 295 300

Trp Leu Phe Ser Phe Asn His Asn Gly His Arg Tyr His Glu Ala Thr
305 310 315 320

Glu Gly Tyr Ser Val Asn Tyr Asp Tyr Asn Gly Lys Gln Tyr Gln Ser
325 330 335

Ser Leu Ala Ala Glu Arg Met Leu Trp Arg Asn Arg Phe His Lys Thr
340 345 350

Ser Val Gly Met Lys Leu Trp Thr Arg Gln Thr Tyr Lys Tyr Ile Asp
355 360 365

Asp Ala Glu Ile Glu Val Gln Arg Arg Arg Ser Ala Gly Trp Glu Ala
370 375 380

Glu Leu Arg His Arg Ala Tyr Leu Asn Arg Trp Gln Leu Asp Gly Lys
385 390 395 400

Leu Ser Tyr Lys Arg Gly Thr Gly Met Arg Gln Ser Met Pro Ala Pro
405 410 415

Glu Glu Asn Gly Gly Gly Thr Ile Pro Gly Thr Ser Arg Met Lys Ile
420 425 430

Ile Thr Ala Gly Leu Asp Ala Ala Ala Pro Phe Met Leu Gly Lys Gln
435 440 445

Gln Phe Phe Tyr Ala Thr Ala Ile Gln Ala Gln Trp Asn Lys Thr Pro
450 455 460

Leu Val Ala Gln Asp Lys Leu Ser Ile Gly Ser Arg Tyr Thr Val Arg
465 470 475 480

Gly Phe Asp Gly Glu Gln Ser Leu Phe Gly Glu Arg Gly Phe Tyr Trp
485 490 495

Gln Asn Thr Leu Thr Trp Tyr Phe His Pro Asn His Gln Phe Tyr Leu
500 505 510

Gly Ala Asp Tyr Gly Arg Val Ser Gly Glu Ser Ala Gln Tyr Val Ser
515 520 525

Gly Lys Gln Leu Met Gly Ala Val Val Gly Phe Arg Gly Gly His Lys
530 535 540

Val Gly Gly Met Phe Ala Tyr Asp Leu Phe Ala Gly Lys Pro Leu His
545 550 555 560

Lys Pro Lys Gly Phe Gln Thr Thr Asn Thr Val Tyr Gly Phe Asn Leu
565 570 575

Asn Tyr Ser Phe
580

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1981 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Peptide

(B) LOCATION: 1..1981

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Met Asn Lys Gly Leu His Arg Ile Ile Phe Ser Lys Lys His Ser Thr
1 5 10 15

Met Val Ala Val Ala Glu Thr Ala Asn Ser Gln Gly Lys Gly Lys Gln
20 25 30

Ala Gly Ser Ser Val Ser Val Ser Leu Lys Thr Ser Gly Asp Leu Cys
35 40 45

Gly Lys Leu Lys Thr Thr Leu Lys Thr Leu Val Cys Ser Leu Val Ser
50 55 60

Leu Ser Met Val Leu Pro Ala His Ala Gln Ile Thr Thr Asp Lys Ser
65 70 75 80

Ala Pro Lys Asn Gln Gln Val Val Ile Leu Lys Thr Asn Thr Gly Ala
85 90 95

Pro Leu Val Asn Ile Gln Thr Pro Asn Gly Arg Gly Leu Ser His Asn
100 105 110

Arg Tyr Thr Gln Phe Asp Val Asp Asn Lys Gly Ala Val Leu Asn Asn
115 120 125

Asp Arg Asn Asn Asn Pro Phe Leu Val Lys Gly Ser Ala Gln Leu Ile
130 135 140

Leu Asn Glu Val Arg Gly Thr Ala Ser Lys Leu Asn Gly Ile Val Thr
145 150 155 160

Val Gly Gly Gln Lys Ala Asp Val Ile Ile Ala Asn Pro Asn Gly Ile
165 170 175

Thr Val Asn Gly Gly Gly Phe Lys Asn Val Gly Arg Gly Ile Leu Thr
180 185 190

Ile Gly Ala Pro Gln Ile Gly Lys Asp Gly Ala Leu Thr Gly Phe Asp
195 200 205

Val Arg Gln Gly Thr Leu Thr Val Gly Ala Ala Gly Trp Asn Asp Lys
210 215 220

Gly Gly Ala Asp Tyr Thr Gly Val Leu Ala Arg Ala Val Ala Leu Gln
225 230 235 240

Gly Lys Leu Gln Gly Lys Asn Leu Ala Val Ser Thr Gly Pro Gln Lys
245 250 255

Val Asp Tyr Ala Ser Gly Glu Ile Ser Ala Gly Thr Ala Ala Gly Thr
260 265 270

Lys Pro Thr Ile Ala Leu Asp Thr Ala Ala Leu Gly Gly Met Tyr Ala
275 280 285

Asp Ser Ile Thr Leu Ile Ala Asn Glu Lys Gly Val Gly Val Lys Asn
290 295 300

Ala Gly Thr Leu Glu Ala Ala Lys Gln Leu Ile Val Thr Ser Ser Gly
305 310 315 320

Arg Ile Glu Asn Ser Gly Arg Ile Ala Thr Thr Ala Asp Gly Thr Glu
325 330 335

Ala Ser Pro Thr Tyr Leu Ser Ile Glu Thr Thr Glu Lys Gly Ala Ala
340 345 350

Gly Thr Phe Ile Ser Asn Gly Gly Arg Ile Glu Ser Lys Gly Leu Leu
355 360 365

Val Ile Glu Thr Gly Glu Asp Ile Ser Leu Arg Asn Gly Ala Val Val
370 375 380

Gln Asn Asn Gly Ser Arg Pro Ala Thr Thr Val Leu Asn Ala Gly His
385 390 395 400

Asn Leu Val Ile Glu Ser Lys Thr Asn Val Asn Asn Ala Lys Gly Ser
405 410 415

Ala Asn Leu Ser Ala Gly Gly Arg Thr Thr Ile Asn Asp Ala Thr Ile
420 425 430

Gln Ala Gly Ser Ser Val Tyr Ser Ser Thr Lys Gly Asp Thr Glu Leu
435 440 445

Gly Glu Asn Thr Arg Ile Ile Ala Glu Asn Val Thr Val Leu Ser Asn
450 455 460

Gly Ser Ile Gly Ser Ala Ala Val Ile Glu Ala Lys Asp Thr Ala His
465 470 475 480

Ile Glu Ser Gly Lys Pro Leu Ser Leu Glu Thr Ser Thr Val Ala Ser
485 490 495

Asn Ile Arg Leu Asn Asn Gly Asn Ile Lys Gly Gly Lys Gln Leu Ala
500 505 510

Leu Leu Ala Asp Asp Asn Ile Thr Ala Lys Thr Thr Asn Leu Asn Thr
515 520 525

Pro Gly Asn Leu Tyr Val His Thr Gly Lys Asp Leu Asn Leu Asn Val
530 535 540

Asp Lys Asp Leu Ser Ala Ala Ser Ile His Leu Lys Ser Asp Asn Ala
545 550 555 560

Ala His Ile Thr Gly Thr Ser Lys Thr Leu Thr Ala Ser Lys Asp Met
565 570 575

Gly Val Glu Ala Gly Leu Leu Asn Val Thr Asn Thr Asn Leu Arg Thr
580 585 590

Asn Ser Gly Asn Leu His Ile Gln Ala Ala Lys Gly Asn Ile Gln Leu
595 600 605

Arg Asn Thr Lys Leu Asn Ala Ala Lys Ala Leu Glu Thr Thr Ala Leu
610 615 620

Gln Gly Asn Ile Val Ser Asp Gly Leu His Ala Val Ser Ala Asp Gly
625 630 635 640

His Val Ser Leu Leu Ala Asn Gly Asn Ala Asp Phe Thr Gly His Asn
645 650 655

Thr Leu Thr Ala Lys Ala Asp Val Asn Ala Gly Ser Val Gly Lys Gly
660 665 670

Arg Leu Lys Ala Asp Asn Thr Asn Ile Thr Ser Ser Ser Gly Asp Ile
675 680 685

Thr Leu Val Ala Gly Asn Gly Ile Gln Leu Gly Asp Gly Lys Gln Arg
690 695 700

Asn Ser Ile Asn Gly Lys His Ile Ser Ile Lys Asn Asn Gly Gly Asn
705 710 715 720

Ala Asp Leu Lys Asn Leu Asn Val His Ala Lys Ser Gly Ala Leu Asn
725 730 735

Ile His Ser Asp Arg Ala Leu Ser Ile Glu Asn Thr Lys Leu Glu Ser
740 745 750

Thr His Asn Thr His Leu Asn Ala Gln His Glu Arg Val Thr Leu Asn
755 760 765

Gln Val Asp Ala Tyr Ala His Arg His Leu Ser Ile Thr Gly Ser Gln
770 775 780

Ile Trp Gln Asn Asp Lys Leu Pro Ser Ala Asn Lys Leu Val Ala Asn
785 790 795 800

Gly Val Leu Ala Leu Asn Ala Arg Tyr Ser Gln Ile Ala Asp Asn Thr
805 810 815

Thr Leu Arg Ala Gly Ala Ile Asn Leu Thr Ala Gly Thr Ala Leu Val
820 825 830

Lys Arg Gly Asn Ile Asn Trp Ser Thr Val Ser Thr Lys Thr Leu Glu
835 840 845

Asp Asn Ala Glu Leu Lys Pro Leu Ala Gly Arg Leu Asn Ile Glu Ala
850 855 860

Gly Ser Gly Thr Leu Thr Ile Glu Pro Ala Asn Arg Ile Ser Ala His
865 870 875 880

Thr Asp Leu Ser Ile Lys Thr Gly Gly Lys Leu Leu Leu Ser Ala Lys
885 890 895

Gly Gly Asn Ala Gly Ala Pro Ser Ala Gln Val Ser Ser Leu Glu Ala
900 905 910

Lys Gly Asn Ile Arg Leu Val Thr Gly Glu Thr Asp Leu Arg Gly Ser
915 920 925

Lys Ile Thr Ala Gly Lys Asn Leu Val Val Ala Thr Thr Lys Gly Lys
930 935 940

Leu Asn Ile Glu Ala Val Asn Asn Ser Phe Ser Asn Tyr Phe Pro Thr
945 950 955 960

Gln Lys Ala Ala Glu Leu Asn Gln Lys Ser Lys Glu Leu Glu Gln Gln
965 970 975

Ile Ala Gln Leu Lys Lys Ser Ser Pro Lys Ser Lys Leu Ile Pro Thr
980 985 990

Leu Gln Glu Glu Arg Asp Arg Leu Ala Phe Tyr Ile Gln Ala Ile Asn
995 1000 1005

Lys Glu Val Lys Gly Lys Lys Pro Lys Gly Lys Glu Tyr Leu Gln Ala
1010 1015 1020

Lys Leu Ser Ala Gln Asn Ile Asp Leu Ile Ser Ala Gln Gly Ile Glu
1025 1030 1035 1040

Ile Ser Gly Ser Asp Ile Thr Ala Ser Lys Lys Leu Asn Leu His Ala
1045 1050 1055

Ala Gly Val Leu Pro Lys Ala Ala Asp Ser Glu Ala Ala Ala Ile Leu
1060 1065 1070

Ile Asp Gly Ile Thr Asp Gln Tyr Glu Ile Gly Lys Pro Thr Tyr Lys
1075 1080 1085

Ser His Tyr Asp Lys Ala Ala Leu Asn Lys Pro Ser Arg Leu Thr Gly
1090 1095 1100

Arg Thr Gly Val Ser Ile His Ala Ala Ala Ala Leu Asp Asp Ala Arg
1105 1110 1115 1120

Ile Ile Ile Gly Ala Ser Glu Ile Lys Ala Pro Ser Gly Ser Ile Asp
1125 1130 1135

Ile Lys Ala His Ser Asp Ile Val Leu Glu Ala Gly Gln Asn Asp Ala
1140 1145 1150

Tyr Thr Phe Leu Lys Thr Lys Gly Lys Ser Gly Lys Ile Ile Arg Lys
1155 1160 1165

Thr Lys Phe Thr Ser Thr Arg Asp His Leu Ile Met Pro Ala Pro Val
1170 1175 1180

Glu Leu Thr Ala Asn Gly Ile Thr Leu Gln Ala Gly Gly Asn Ile Glu
1185 1190 1195 1200

Ala Asn Thr Thr Arg Phe Asn Ala Pro Ala Gly Lys Val Thr Leu Val
1205 1210 1215

Ala Gly Glu Glu Leu Gln Leu Leu Ala Glu Glu Gly Ile His Lys His
1220 1225 1230

Glu Leu Asp Val Gln Lys Ser Arg Arg Phe Ile Gly Ile Lys Val Gly
1235 1240 1245

Lys Ser Asn Tyr Ser Lys Asn Glu Leu Asn Glu Thr Lys Leu Pro Val
1250 1255 1260

Arg Val Val Ala Gln Thr Ala Ala Thr Arg Ser Gly Trp Asp Thr Val
1265 1270 1275 1280

Leu Glu Gly Thr Glu Phe Lys Thr Thr Leu Ala Gly Ala Asp Ile Gln
1285 1290 1295

Ala Gly Val Gly Glu Lys Ala Arg Val Asp Ala Lys Ile Ile Leu Lys
1300 1305 1310

Gly Ile Val Asn Arg Ile Gln Ser Glu Glu Lys Leu Glu Thr Asn Ser
1315 1320 1325

Thr Val Trp Gln Lys Gln Ala Gly Arg Gly Ser Thr Ile Glu Thr Leu
1330 1335 1340

Lys Leu Pro Ser Phe Glu Ser Pro Thr Pro Pro Lys Leu Ser Ala Pro
1345 1350 1355 1360

Gly Gly Tyr Ile Val Asp Ile Pro Lys Gly Asn Leu Lys Thr Glu Ile
1365 1370 1375

Glu Lys Leu Ser Lys Gln Pro Glu Tyr Ala Tyr Leu Lys Gln Leu Gln
1380 1385 1390

Val Ala Lys Asn Ile Asn Trp Asn Gln Val Gln Leu Ala Tyr Asp Arg
1395 1400 1405

Trp Asp Tyr Lys Gln Glu Gly Leu Thr Glu Ala Gly Ala Ala Ile Ile
1410 1415 1420

Ala Leu Ala Val Thr Val Val Thr Ser Gly Ala Gly Thr Gly Ala Val
1425 1430 1435 1440

Leu Gly Leu Asn Gly Ala Ala Ala Ala Ala Thr Asp Ala Ala Phe Ala
1445 1450 1455

Ser Leu Ala Ser Gln Ala Ser Val Ser Phe Ile Asn Asn Lys Gly Asp
1460 1465 1470

Val Gly Lys Thr Leu Lys Glu Leu Gly Arg Ser Ser Thr Val Lys Asn
1475 1480 1485

Leu Val Val Ala Ala Ala Thr Ala Gly Val Ala Asp Lys Ile Gly Ala
1490 1495 1500

Ser Ala Leu Asn Asn Val Ser Asp Lys Gln Trp Ile Asn Asn Leu Thr
1505 1510 1515 1520

Val Asn Leu Ala Asn Ala Gly Ser Ala Ala Leu Ile Asn Thr Ala Val
1525 1530 1535

Asn Gly Gly Ser Leu Lys Asp Asn Leu Glu Ala Asn Ile Leu Ala Ala
1540 1545 1550

Leu Val Asn Thr Ala His Gly Glu Ala Ala Ser Lys Ile Lys Gln Leu
1555 1560 1565

Asp Gln His Tyr Ile Val His Lys Ile Ala His Ala Ile Ala Gly Cys
1570 1575 1580

Ala Ala Ala Ala Ala Asn Lys Gly Lys Cys Gln Asp Gly Ala Ile Gly
1585 1590 1595 1600

Ala Ala Val Gly Glu Ile Val Gly Glu Ala Leu Thr Asn Gly Lys Asn
1605 1610 1615

Pro Asp Thr Leu Thr Ala Lys Glu Arg Glu Gln Ile Leu Ala Tyr Ser
1620 1625 1630

Lys Leu Val Ala Gly Thr Val Ser Gly Val Val Gly Gly Asp Val Asn
1635 1640 1645

Ala Ala Ala Asn Ala Ala Glu Val Ala Val Lys Asn Asn Gln Leu Ser
1650 1655 1660

Asp Lys Glu Gly Arg Glu Phe Asp Asn Glu Met Thr Ala Cys Ala Lys
1665 1670 1675 1680

Gln Asn Asn Pro Gln Leu Cys Arg Lys Asn Thr Val Lys Lys Tyr Gln
1685 1690 1695

Asn Val Ala Asp Lys Arg Leu Ala Ala Ser Ile Ala Ile Cys Thr Asp
1700 1705 1710

Ile Ser Arg Ser Thr Glu Cys Arg Thr Ile Arg Lys Gln His Leu Ile
1715 1720 1725

Asp Ser Arg Ser Leu His Ser Ser Trp Glu Ala Gly Leu Ile Gly Lys
1730 1735 1740

Asp Asp Glu Trp Tyr Lys Leu Phe Ser Lys Ser Tyr Thr Gln Ala Asp
1745 1750 1755 1760

Leu Ala Leu Gln Ser Tyr His Leu Asn Thr Ala Ala Lys Ser Trp Leu
1765 1770 1775

Gln Ser Gly Asn Thr Lys Pro Leu Ser Glu Trp Met Ser Asp Gln Gly
1780 1785 1790

Tyr Thr Leu Ile Ser Gly Val Asn Pro Arg Phe Ile Pro Ile Pro Arg
1795 1800 1805

Gly Phe Val Lys Gln Asn Thr Pro Ile Thr Asn Val Lys Tyr Pro Glu
1810 1815 1820

Gly Ile Ser Phe Asp Thr Asn Leu Lys Arg His Leu Ala Asn Ala Asp
1825 1830 1835 1840

Gly Phe Ser Gln Glu Gln Gly Ile Lys Gly Ala His Asn Arg Thr Asn
1845 1850 1855

Phe Met Ala Glu Leu Asn Ser Arg Gly Gly Arg Val Lys Ser Glu Thr
1860 1865 1870

Gln Thr Asp Ile Glu Gly Ile Thr Arg Ile Lys Tyr Glu Ile Pro Thr
1875 1880 1885

Leu Asp Arg Thr Gly Lys Pro Asp Gly Gly Phe Lys Glu Ile Ser Ser
1890 1895 1900

Ile Lys Thr Val Tyr Asn Pro Lys Lys Phe Ser Asp Asp Lys Ile Leu
1905 1910 1915 1920

Gln Met Ala Gln Asn Ala Ala Ser Gln Gly Tyr Ser Lys Ala Ser Lys
1925 1930 1935

Ile Ala Gln Asn Glu Arg Thr Lys Ser Ile Ser Glu Arg Lys Asn Val
1940 1945 1950

Ile Gln Phe Ser Glu Thr Phe Asp Gly Ile Lys Phe Arg Ser Tyr Phe
1955 1960 1965

Asp Val Asn Thr Gly Arg Ile Thr Asn Ile His Pro Glu
1971 1975 1980

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 143 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..143

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Met Lys Asn Asn Ile Phe Leu Asn Leu Asn Lys Lys Ser Ile Asn Asn
1 5 10 15

Asn His Phe Val Ile Ser Ile Phe Phe Glu Thr Ile Tyr Gln Phe Glu
20 25 30

Thr Lys Asp Thr Leu Leu Glu Cys Phe Lys Asn Ile Thr Thr Thr Gly
35 40 45

His Phe Gly Val Ile Gly Ala Gln Tyr Glu Lys Ile Asp Ala Thr Arg
50 55 60

Trp Ile Gly Asp Tyr Glu Glu Val Asn Gly Phe Glu Tyr Ile Asp Lys
65 70 75 80

Ala Pro Ser Ile Tyr Phe Ser Val Gly Asp Asp Phe Asn Pro Glu Glu
85 90 95

Leu Ile Ile Pro Ile Asn Leu Ala Tyr His Tyr Phe Asn Ile Ala Ile
100 105 110

Ser Asp Phe Leu Ile Ala His Pro Glu Tyr Gln Lys Lys Cys Lys Glu
115 120 125

Ile Gln Lys Thr Tyr Ser Gln Thr Asn Cys Ser Leu His Glu Thr
130 135 140

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 833 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..833

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

```
Val Leu Lys Thr Pro Pro Thr Leu Ala Ala Glu Leu Ser Gly Lys Thr
1               5                  10                  15

Gly Val Ser Ile Ser Ala Pro Tyr Ala Asn Glu Asn Ser Arg Ile Leu
            20                  25                  30

Leu Ser Thr Thr Asp Ile Ser Ser Glu Asn Gly Lys Ile Lys Ile Gln
        35                  40                  45

Ser Tyr Gly Asp Gln Tyr Tyr Tyr Ala Arg Gln Ser Glu Leu Tyr Thr
    50                  55                  60

Phe Glu Arg Arg Ser Tyr Lys Thr Gly Lys Trp Tyr Asn Arg Lys His
65                  70                  75                  80

Ile Thr Glu Val Lys Glu His Lys Asn Ala Lys Pro Asp Ala Val Asn
                85                  90                  95

Leu Ser Ala Ser Gln Gly Ile Asp Ile Lys Ser Gly Gly Ser Ile Asp
            100                 105                 110

Ala Tyr Ala Thr Ala Phe Asp Ala Pro Lys Gly Ser Ile Asn Ile Glu
        115                 120                 125

Ala Gly Arg Lys Leu Thr Leu Tyr Ala Val Glu Glu Leu Asn Tyr Asp
    130                 135                 140

Lys Leu Asp Ser Gln Lys Arg Arg Arg Phe Leu Gly Ile Ser Tyr Ser
145                 150                 155                 160

Lys Ala His Asp Thr Thr Thr Gln Val Met Lys Thr Ala Leu Pro Ser
                165                 170                 175

Arg Val Val Ala Glu Ser Ala Asn Leu Gln Ser Gly Trp Asp Thr Lys
            180                 185                 190
```

Leu Gln Gly Thr Gln Phe Glu Thr Thr Leu Gly Gly Ala Thr Ile Arg
195 200 205

Ala Gly Val Gly Glu Gln Ala Arg Ala Asp Ala Lys Ile Ile Leu Glu
210 215 220

Gly Ile Lys Ser Ser Ile His Thr Glu Thr Val Ser Ser Ser Lys Ser
225 230 235 240

Thr Leu Trp Gln Lys Gln Ala Gly Arg Gly Ser Asn Ile Glu Thr Leu
245 250 255

Gln Leu Pro Ser Phe Thr Gly Pro Val Ala Pro Val Leu Ser Ala Pro
260 265 270

Gly Gly Tyr Ile Val Asp Ile Pro Lys Gly Asn Leu Lys Thr Gln Ile
275 280 285

Glu Thr Leu Thr Lys Gln Pro Glu Tyr Ala Tyr Leu Lys Gln Leu Gln
290 295 300

Val Ala Lys Asn Ile Asn Trp Asn Gln Val Gln Leu Ala Tyr Asp Lys
305 310 315 320

Trp Asp Tyr Lys Gln Glu Gly Met Thr Pro Ala Ala Ala Ala Val Val
325 330 335

Val Ile Val Val Thr Val Leu Thr Tyr Gly Ala Leu Ser Ala Pro Ala
340 345 350

Ala Ala Gly Thr Ala Gly Ala Ala Gly Ala Gly Ala Gly Gly Ala Ala
355 360 365

Ala Gly Thr Ala Ala Gly Thr Gly Val Ala Ala Gly Thr Ala Ala Thr
370 375 380

Thr Gly Val Ala Ala Gly Thr Ser Ala Ala Ala Ile Thr Thr Ala Ala
385 390 395 400

Gly Lys Ala Ala Leu Ala Ser Leu Ala Ser Gln Ala Ala Val Ser Leu
405 410 415

Ile Asn Asn Lys Gly Asp Ile Asn His Thr Leu Lys Glu Leu Gly Lys
420 425 430

Ser Ser Thr Val Arg Gln Ala Ala Thr Ala Ala Val Thr Ala Gly Val
435 440 445

Leu Gln Gly Ile Ser Gly Leu Asn Thr Gln Ala Ala Glu Ala Val Ser
450 455 460

Lys His Phe His Ser Pro Ala Ala Gly Lys Leu Thr Ala Asn Leu Ile
465 470 475 480

Asn Ser Thr Ala Ala Ala Ser Val His Thr Ala Ile Asn Gly Gly Ser
485 490 495

Leu Lys Asp Asn Leu Gly Asp Ala Ala Leu Gly Ala Ile Val Ser Thr
500 505 510

Val His Gly Glu Val Ala Ser Lys Ile Lys Phe Asn Leu Ser Glu Asp
515 520 525

Tyr Ile Ala His Lys Ile Ala His Ala Val Ala Gly Cys Ala Ser Ala
530 535 540

Val Ala Asn Lys Gly Lys Cys Arg Asp Gly Ala Ile Gly Ala Ala Val
545 550 555 560

Gly Glu Met Val Gly Glu Thr Leu Leu Asp Gly Arg Asp Val Gly Lys
565 570 575

Leu Ser Pro Gln Glu Arg Gln Lys Val Ile Ala Tyr Ser Gln Ile Ile
580 585 590

Ala Gly Ser Ala Val Ala Leu Val Lys Gly Asp Val Asn Thr Ala Val
595 600 605

Asn Ala Ala Thr Val Ala Val Glu Asn Asn Ser Leu Leu Ala Arg Arg
610 615 620

Arg Val Asn Ile Arg Trp Thr Pro Arg Gln Glu Leu Glu His Glu Tyr
625 630 635 640

Ala Ile Leu Glu Ile Gln Ala Ile Thr Asn Gln Ile Arg Arg Leu Asp
645 650 655

Pro Lys Phe Asn Gly Ile Ala Ile Leu Arg Thr Pro Gly Glu Pro Trp
660 665 670

Thr Arg His Asp Val Gln Thr Tyr Arg Gln Tyr Tyr Asn Gln Leu Arg
675 680 685

Glu Ser Arg Gly Phe Ala Val Glu Pro Ile Tyr Arg Ile Arg Ile Asn
690 695 700

Asn Gly Asn Glu Phe Asn Arg Ile Met Ser Ser Lys Tyr Pro Tyr Asn
705 710 715 720

Glu Leu Tyr Val Ala Asn Pro Lys Ser Ala Thr Gly Tyr Phe Arg Val
725 730 735

Asp Ser Tyr Asp Pro Ala Thr Arg Glu Ile Ile Ser Arg Lys Phe Thr
740 745 750

Gln Phe Ser Gln Ile Gln Glu Ser Thr Gly Ile Gly Tyr Ile Lys Glu
755 760 765

Ala Val Arg Lys Tyr Ser Pro Gly Thr Val Ile Ser Asn Val Pro Ser
770 775 780

Thr Pro Thr Thr Ile Arg Gly Arg Lys Leu Glu Gly Lys Leu Ile Leu
785 790 795 800

Glu Val Pro Ala Gln Val Asn Pro Ile Pro Gln Ser Val Leu Arg Ala
805 810 815

Ala Gln Glu Glu Asn Val Ile Ile Arg Asp Thr Thr Gly Arg Ile Tyr
820 825 830

Lys

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 833 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Val Leu Lys Thr Pro Pro Thr Leu Ala Ala Glu Leu Ser Gly Lys Thr
1 5 10 15

Gly Val Ser Ile Ser Ala Pro Tyr Ala Asn Glu Asn Ser Arg Ile Leu
20 25 30

Leu Ser Thr Thr Asp Ile Ser Ser Glu Asn Gly Lys Ile Lys Ile Gln
35 40 45

Ser Tyr Gly Asp Gln Tyr Tyr Tyr Ala Arg Gln Ser Glu Leu Tyr Thr
50 55 60

Phe Glu Arg Arg Ser Tyr Lys Thr Gly Lys Trp Tyr Asn Arg Lys His
65 70 75 80

Ile Thr Glu Val Lys Glu His Lys Asn Ala Lys Pro Asp Ala Val Asn
85 90 95

Leu Ser Ala Ser Gln Gly Ile Asp Ile Lys Ser Gly Gly Ser Ile Asp
100 105 110

Ala Tyr Ala Thr Ala Phe Asp Ala Pro Lys Gly Ser Ile Asn Ile Glu
115 120 125

Ala Gly Arg Lys Leu Thr Leu Tyr Ala Val Glu Glu Leu Asn Tyr Asp
130 135 140

Lys Leu Asp Ser Gln Lys Arg Arg Arg Phe Leu Gly Ile Ser Tyr Ser
145 150 155 160

Lys Ala His Asp Thr Thr Thr Gln Val Met Lys Thr Ala Leu Pro Ser
165 170 175

Arg Val Val Ala Glu Ser Ala Asn Leu Gln Ser Gly Trp Asp Thr Lys
180 185 190

Leu Gln Gly Thr Gln Phe Glu Thr Thr Leu Gly Gly Ala Thr Ile Arg
195 200 205

Ala Gly Val Gly Glu Gln Ala Arg Ala Asp Ala Lys Ile Ile Leu Glu
210 215 220

Gly Ile Lys Ser Ser Ile His Thr Glu Thr Val Ser Ser Ser Lys Ser
225 230 235 240

Thr Leu Trp Gln Lys Gln Ala Gly Arg Gly Ser Asn Ile Glu Thr Leu
245 250 255

Gln Leu Pro Ser Phe Thr Gly Pro Val Ala Pro Val Leu Ser Ala Pro
260 265 270

Gly Gly Tyr Ile Val Asp Ile Pro Lys Gly Asn Leu Lys Thr Gln Ile
275 280 285

```
Glu Thr Leu Thr Lys Gln Pro Glu Tyr Ala Tyr Leu Lys Gln Leu Gln
    290                 295                 300

Val Ala Lys Asn Ile Asn Trp Asn Gln Val Gln Leu Ala Tyr Asp Lys
305                 310                 315                 320

Trp Asp Tyr Lys Gln Glu Gly Met Thr Pro Ala Ala Ala Ala Val Val
                325                 330                 335

Val Ile Val Val Thr Val Leu Thr Tyr Gly Ala Leu Ser Ala Pro Ala
            340                 345                 350

Ala Ala Gly Thr Ala Gly Ala Ala Gly Ala Gly Ala Gly Gly Ala Ala
        355                 360                 365

Ala Gly Thr Ala Ala Gly Thr Gly Val Ala Ala Gly Thr Ala Ala Thr
    370                 375                 380

Thr Gly Val Ala Ala Gly Thr Ser Ala Ala Ala Ile Thr Thr Ala Ala
385                 390                 395                 400

Gly Lys Ala Ala Leu Ala Ser Leu Ala Ser Gln Ala Ala Val Ser Leu
                405                 410                 415

Ile Asn Asn Lys Gly Asp Ile Asn His Thr Leu Lys Glu Leu Gly Lys
            420                 425                 430

Ser Ser Thr Val Arg Gln Ala Ala Thr Ala Ala Val Thr Ala Gly Val
        435                 440                 445

Leu Gln Gly Ile Ser Gly Leu Asn Thr Gln Ala Ala Glu Ala Val Ser
    450                 455                 460

Lys His Phe His Ser Pro Ala Ala Gly Lys Leu Thr Ala Asn Leu Ile
465                 470                 475                 480

Asn Ser Thr Ala Ala Ala Ser Val His Thr Ala Ile Asn Gly Gly Ser
                485                 490                 495
```

Leu Lys Asp Asn Leu Gly Asp Ala Ala Leu Gly Ala Ile Val Ser Thr
500 505 510

Val His Gly Glu Val Ala Ser Lys Ile Lys Phe Asn Leu Ser Glu Asp
515 520 525

Tyr Ile Ala His Lys Ile Ala His Ala Val Ala Gly Cys Ala Ser Ala
530 535 540

Val Ala Asn Lys Gly Lys Cys Arg Asp Gly Ala Ile Gly Ala Ala Val
545 550 555 560

Gly Glu Met Val Gly Glu Thr Leu Leu Asp Gly Arg Asp Val Gly Lys
565 570 575

Leu Ser Pro Gln Glu Arg Gln Lys Val Ile Ala Tyr Ser Gln Ile Ile
580 585 590

Ala Gly Ser Ala Val Ala Leu Val Lys Gly Asp Val Asn Thr Ala Val
595 600 605

Asn Ala Ala Thr Val Ala Val Glu Asn Asn Ser Leu Leu Ala Arg Arg
610 615 620

Arg Val Asn Ile Arg Trp Thr Pro Arg Gln Glu Leu Glu His Glu Tyr
625 630 635 640

Ala Ile Leu Glu Ile Gln Ala Ile Thr Asn Gln Ile Arg Arg Leu Asp
645 650 655

Pro Lys Phe Asn Gly Ile Ala Ile Leu Arg Thr Pro Gly Glu Pro Trp
660 665 670

Thr Arg His Asp Val Gln Thr Tyr Arg Gln Tyr Tyr Asn Gln Leu Arg
675 680 685

Glu Ser Arg Gly Phe Ala Val Glu Pro Ile Tyr Arg Ile Arg Ile Asn
690 695 700

Asn Gly Asn Glu Phe Asn Arg Ile Met Ser Ser Lys Tyr Pro Tyr Asn
705 710 715 720

Glu Leu Tyr Val Ala Asn Pro Lys Ser Ala Thr Gly Tyr Phe Arg Val
725 730 735

Asp Ser Tyr Asp Pro Ala Thr Arg Glu Ile Ile Ser Arg Lys Phe Thr
740 745 750

Gln Phe Ser Gln Ile Gln Glu Ser Thr Gly Ile Gly Tyr Ile Lys Glu
755 760 765

Ala Val Arg Lys Tyr Ser Pro Gly Thr Val Ile Ser Asn Val Pro Ser
770 775 780

Thr Pro Thr Thr Ile Arg Gly Arg Lys Leu Glu Gly Lys Leu Ile Leu
785 790 795 800

Glu Val Pro Ala Gln Val Asn Pro Ile Pro Gln Ser Val Leu Arg Ala
805 810 815

Ala Gln Glu Glu Asn Val Ile Ile Arg Asp Thr Thr Gly Arg Ile Tyr
820 825 830

Lys

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..162

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Met Lys Lys Asp Ile Phe Tyr Cys Glu Gln Trp Ser Tyr Gly Tyr Lys
1 5 10 15

Arg Leu His Lys Pro Phe Ser Glu Lys Gln Ala Glu Glu Lys His Leu
20 25 30

Lys Gly Glu Leu Tyr Thr Ala Val Ile Gly Ser Ala Thr Gln Pro Glu
35 40 45

Tyr Val Ile Thr Leu Arg Glu Glu Val Gly Phe Phe Ser Val Asn Phe
50 55 60

Phe Asp Lys Phe Gly Arg Asp Tyr Leu Thr His Gln Phe Gln Lys Tyr
65 70 75 80

Ser Asn Ser Asn Tyr Tyr Phe Leu Ser Met Ala Val Trp Arg Asp Tyr
85 90 95

Ile Thr Leu Glu Ser His Asp Leu Ala Glu Gly Tyr Thr Tyr Phe Phe
100 105 110

Asn Glu Asn Thr Asp Asp Cys Tyr Val Leu Lys Gln Asp Phe Ile Asn
115 120 125

Asn Glu Arg Tyr Glu Lys Thr Glu Leu Tyr Ser Gln Lys Asp Lys Val
130 135 140

Ile Leu Phe Pro Lys Phe Gly Glu Tyr Asp Leu Val Leu Asn Pro Asp
145 150 155 160

Ile Ile

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 90 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..90

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Met Asn Lys Arg Met Lys Met Cys Pro Ala Cys Gln Gln Gly Tyr Leu
1 5 10 15

Tyr His Ser Lys Pro Lys Tyr Leu His Asp Glu Ile Ile Leu Cys Asp
20 25 30

Glu Cys Asp Ala Val Trp Leu Lys Gly Met Asn Ile Phe Tyr Gly Glu
35 40 45

Tyr Glu Lys Asp Phe Tyr Ser Tyr Val Pro Phe Met Glu Ser Gln Gly
50 55 60

Ile Thr Ser Glu Cys Ile Trp Glu Gly Asp Leu Phe Asp His Pro Tyr
65 70 75 80

Tyr Glu Asp Glu Asn Ser Asn Asp Met Asp
85 90

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 313 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..313

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Met Ser Ala Thr Glu Ile Glu Lys Ala Lys Ala Lys Ile Thr Ala Tyr
1 5 10 15

Ser Lys Leu Val Ala Gly Thr Ala Ser Ala Val Val Gly Gly Asp Val
20 25 30

Asn Thr Ala Ala Asn Ala Ala Gln Ile Ala Val Glu Asn Asn Thr Leu
35 40 45

Tyr Pro Arg Cys Val Gly Ala Lys Cys Asp Glu Phe Gln Lys Glu Gln
50 55 60

Gln Lys Trp Ile Arg Glu Asn Pro Glu Glu Tyr Arg Glu Val Leu Leu
65 70 75 80

Phe Gln Thr Gly Phe Ile Pro Ile Ile Gly Asp Ile Gln Ser Phe Val
85 90 95

Gln Ala Gln Thr Ala Ala Asp His Leu Phe Ala Leu Leu Gly Val Val
100 105 110

Pro Gly Ile Gly Glu Ser Ile Gln Ala Tyr Lys Val Ala Lys Ala Ala
115 120 125

Lys Asn Leu Gln Gly Met Lys Lys Ala Leu Asp Lys Ala Ala Thr Val
130 135 140

Ala Thr Ala Gln Gly Tyr Val Ser Lys Thr Lys Ile Lys Ile Gly Gln
145 150 155 160

Thr Glu Leu Arg Val Thr Ala Ala Thr Asp Lys Gln Leu Leu Lys Ala
165 170 175

Ile Gly Glu Gly Arg Asp Thr Thr Gly Lys Met Thr Glu Gln Leu Phe
180 185 190

Asp Ser Leu Ala Lys Gln Asn Gly Phe Arg Val Leu Ser Gly Gly Lys
195 200 205

Tyr Gly Gly Asn Asn Gly Phe Asp His Val Trp Gln Ala Ala Asp Gly
210 215 220

Ser Val Val Leu Ile Val Glu Ser Lys Gln Ile Arg Asn Gly Thr Val
225 230 235 240

Gln Leu Asn Pro Asn Gly Ala Gly Gly Tyr Thr Gln Met Ser Glu Asp
245 250 255

Trp Ile Arg Gln Val Leu Asp Gln Leu Pro Asp Gly Ser Pro Ala Lys
260 265 270

Ala Ala Val Phe Lys Ala Asn Lys Asn Gly Thr Leu Lys Thr Ala Ile
275 280 285

Ala Gly Val Asp Arg Gln Thr Gly Lys Ala Val Ile Leu Pro Val Lys
290 295 300

Val Pro Ser Lys Thr Asn Ile Arg Arg
305 310

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 311 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..311

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Met Gly His Asn Met Met Thr Thr Gln Lys Trp Tyr Glu His Ile Thr
1 5 10 15

Asn Val Ile Ile Gly Asn Thr Ala Asn Phe Asn Ser Gly Cys Leu Asp
20 25 30

Ser Ile Asp Tyr Val Asp Glu Arg Lys Gly Val Pro Leu Ala Ala Met
35 40 45

Gln His Ile Phe Met Asp Val Arg Ala Ala Ala Ser His Ala Tyr Leu
50 55 60

Phe Glu His Asp Leu Lys Lys Phe Lys Gln Tyr Ala Tyr Val Ala Gly
65 70 75 80

Lys Leu Gly Val Leu Leu Ser Val Asn Ser Thr Asp Pro Glu Pro Phe
85 90 95

Phe Phe Pro Cys Asp Met Leu Asn Ile Gln Asn Pro Met Phe Leu Met
100 105 110

Leu Met Ser Asp Ser Pro Gln Leu Arg Glu Phe Leu Val Arg Asn Ile
115 120 125

Asp Asn Ile Ala Asn Asp Thr Glu Ala Phe Ile Asn Arg Tyr Asp Leu
130 135 140

Asn Arg His Met Ile Tyr Asn Thr Leu Leu Met Val Glu Gly Lys Gln
145 150 155 160

Leu Asp Arg Leu Lys Gln Arg Ser Glu Lys Val Leu Ala His Pro Thr
165 170 175

Pro Ser Lys Trp Leu Gln Lys Arg Leu Tyr Asp Tyr Arg Phe Phe Leu
180 185 190

Ala Phe Ala Glu Gln Asp Ala Glu Ala Met Lys Ala Ala Leu Glu Pro
195 200 205

Leu Phe Asp Lys Lys Thr Ala Arg Met Ala Ala Lys Glu Thr Leu Ser
210 215 220

Tyr Phe Asp Phe Tyr Leu Gln Pro Gln Ile Val Thr Tyr Ala Lys Ile
225 230 235 240

Ala Ser Met His Gly Phe Asp Leu Gly Ile Asp Gln Glu Ile Ser Pro
245 250 255

Arg Asp Leu Ile Val Tyr Asp Pro Leu Pro Ala Asp Glu Tyr Gln Asp
260 265 270

Ile Phe Asp Phe Met Lys Gln Tyr Asp Leu Ser Tyr Pro Tyr Glu Tyr
275 280 285

Leu Gln Asp Trp Ile Asp Tyr Tyr Thr Phe Lys Thr Asp Lys Leu Val
290 295 300

Phe Gly Asn Ala Lys Arg Glu
305 310

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

GCCACCGGTA CGGAAACTGA A 21

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

CCTGAATTCA TGTCTATTCC ATTTTGAAGA 30

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

CCGAGATCTT TAACCCTTTG GGCTTAAGCG A 31

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

GGGAGATCTC CGCTCGTGT TGTGCATTA 29

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

AAGAGATCTG CAGCCAAGGC TCTCGAAA 28

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

GGGAGATCTC AGGCTGCCGC CGTTGA 26

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

GGGAGATCTC ACCCCAAGAA CGCCAAAA 28

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

GGGAGATCTG AACGTATAGT AATCTATCCA A 31

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

AGTGGCTCCT AG 12

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

AGCACTCTCC AGCCTCTCAC CGAG 24

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

AGTGGCTCTT AA 12

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

AGTGGCTGGC 10

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AGCACTCTCC AGCCTCTCAC CGAC 24

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 base pairs

(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

GTACTTGCCT AG 12

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

ACCGACGTCG ACTATCCATG AACG 24

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

GTACTTGCTT AA 12

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

GTACTTGGGC 10

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

ACCGACGTCG ACTATCCATG AACC 24

(2) INFORMATION FOR SEQ ID NO: 64

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

AATTCTCCCT CG

(2) INFORMATION FOR SEQ ID NO: 65

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

AGGCAACTGT GCTATCCGAG GGAG

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 140 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

GATCAACTTT TCCCTGTTTG TCCCATTACC GGTTTGAATG AACCGATTGC GCGCCGCGCG 60

TGTTGTTGGA CATTACCTGC GATTCAGACG GTACGATTGA CCACTACATC GAGGAGAACG 120

GCAATCAGGG TACAATGCTA 140

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 192 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

GATCCGCGTA CTTGGTTTTT CATATTTTGC ATAGTCTTGT CGGTCGGGCA TCTTCCCCGA 60

CATCATCTAA ATTTGTCTTT ATTGGTTTTT ACGCCACTCA TTGCGGATAA ACAATATTCC 120

GCCTTGCCGT CGCGAATGTT CAAGCTAGCC TGCATCACCG TAATCAGGTT GCCCGTTACC 180

GAGCCTTCGA GA 192

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 188 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

GATCCGGCTG CCCGACGCGC GCAAAATTGC CGCCGAGGAA AGCGCGCACA ACCACGACGG 60

CAAAACCAGC GTATGGCAAT ACAAACATCT CGTGTTCGGT ACGGCAGGCA TTTTCTGCTA 120

TGTCGGCGCG GAGGTGTCTA TCGGTTCGTT GATGGTCAAC GTATTGGGTT ATCTGAAAGG 180

GCTGGATC 188

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

GATCCCCCAC TTTACCTCGG GCAGATTTTG CGCGTTCATT ACAATAGCGT ATTTATGCGT 60

TTGCGTTTGC GCTTGCCGCT GCCCCCCCCC CGCCGGTATG GGAAAACATC AATATGGCGG 120

TATAAAGCGC GGTATGGCGG AAAACCTGCC GTTTCCAAGT TTTATTCATC TTTTATTCCT 180

TGAGTTTGCC TTCACGGGAC GGGGCGGCGC GCGGAACGCG GGGTTCGGTA AACCGCCCGA 240

TTCCGCGCCC GCCGAATTGC TGATTGAAAA GCTTACTTCC CCATTTTAAC TTTGCACACT 300

GATC 304

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 243 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

GATCAGACCC ATTTTCAGCG CACCGTAAGC GCGGATTTTC TCGAATTTTT CCAAAGCTGC 60

GGCATCGTTG TTGATGTCGT CTTGCAACTC TTTGCCCGTG TAGCCCAAGT CGGCGGCATT 120

CAGGAAAACG GTCGGAATGC CCGCGTTGAT GAGCGTGGCT TTCAAACGGC CTATATTCGG 180

CACATCAATT TCATCGACCA AATTGCCGGT TGGGAACATA CTGCCTTCGC CGTCGGCTGG 240

ATC 243

(2) INFORMATION FOR SEQ ID NO: 71

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 236 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

CGGCGGCGTAGTccgccGcgACAGCGTTACCATAAGCGGGACAGACTACACCCCTTTATCTAACCCGC
AAAGTTTGGATACGGAATTAAAATGGTTGCTTCAAGAAGCTCCCGAAATAGAAAATCCTTTCGACCGC
GCCGTTTATCTCCATAATAATTTGGCGTATCTTCAATATTTTAAAGATTGCAATAAACGTACTGCCAG
AAACTGCATGACCTTGTCGCTGATGCGCTCCG

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 280 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

CGGTCAATCA CAAGAAAGTC AGCCGTCTGA TGGCGAAGAC GGGGCTGAAG GCAGTGATAT 60

GGCGGCGCAA ATACCGCTCG TTCAAAGGAG AAGTCGGCAA AATTGCGCCG AATATCCTGC 120

GACGCTGTTT CCATGCAGAA AAGCCGAATG AGAAATGGGT AACGGACGTT GCCGAGTTCA 180

ATGTAGGCGG AGAAAAGATA TACCTTTCTC CGATTATGGA TTTGTTTAAC GGGGAAATCG 240

TCAGTTACCG TATTCAGACC CGCCCGACTT TCGATTTGGC 280

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

CGGTCAGAAA CAGGCAAGGT AATGAAAATG CCTGAGGCAC GGACTGTGCT GCGAACGAAA 60

ACTCCTTACC GAAGTCTTCT ATACCCAGGC TCAATAGCCG CTCAAGGAGA GAGCTATCAT 120

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

CGGTCAGAAA CAGGCAAGGT AATGAAAATG CCTGAGGCAC GGACTGTGCT GCGAACGAAA 60

ACTCCTTACC GAAGTCTTCT ATACCCAGGC TCAATAGCCG CTCAAGGAGA GAGCTATCAT 120

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 152 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

CGGTGTTTTT CTTAACAATT CGCCGACTTC ATGGCGATAT TTAAGTGACA GTTGCTCCGC 60

CCACGCAGTT GCGCCGAACT CAGCACCACG ACATTATACT GATTATGCAC ATCGGCAAGA 120

TCAAACTGAC CTATCGTAGT ATCGCAGACT GT 152

(2) INFORMATION FOR SEQ ID NO: 76

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 381 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

CGGGAGGTTTTGTGCATCCTGATACCGATCGGTTGTTGTTGCTCAAAGGACAGAAGGCCGCTGATAAA
CGAGATTACCTGTTTGTCGCTATTGACGATTTTTATACTCTGCCATTTTGCCAGACAAAACCGCAGAC
AGTGCTGCCAAGTTTCTGACCGAACATCTGGCCGACCCCTGCTTGTACCTGATTGAGTACGCTTACTC
TGACAATGATAGGTAATATAAAGAGCCGTCCAACATGCTTTCGGTGCAGTTTGTTATGATAATGGGAT
TGGTTGGAGGCTTGCCCGATTTGCTTGTCCGCAGACCAACGGTAAGGCGGAGCGGGTTATCCGTACCT
TGATGGAGATGTGGCATGAGGAACAGTCGTTTGACAGACCG

(2) INFORMATION FOR SEQ ID NO: 77

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 269 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

CGGAGCATAA AATCGTTATT AAAGATAATG GTATAGGAAC GAGCTTCGAT GAAATCAATG 60

ATTTTTATTT GAGAATCGGT CGGAACAGAA GGGAAGAAAA ACAAGCCTCC CCGTGCGGAA 120

GAATTCCAAC GGGTAAAAAA GGCCTTGGTA AATTGGCATT ATTCGGGCTT GGCAACAAAA 180

TTGAAATTTC TACTATCCAG GGAAACGAAA GGGTTACTTT TACTTTGGAT TATGCAGAGA 240

TTCGAAGAAG CAAGGGTATT TATCAACCG 269

(2) INFORMATION FOR SEQ ID NO: 78

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 203 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

CGGATGAAAACGGCATACGCgcCAAAGTATTTACGAACATCAaAGGCTTGAAGATACCGCACACCTAC
ATAGAAACGGACGCGAAAAAGCTGCCGAAATCGACAGATGAGCAGCTTTCGGCGCATGATATGTACGA
ATGGATAAAGAAGCCCGAAAATATCGGGTCTATTGTCATTGTAGATGAAGCTCAAGACGTATGGCCG

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 229 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79

CGGTTTCAGG TTGTCGCGAA GGCTCGGTAA CGGGCAACCT GATTACGGGT GATGCAGGCA 60

GCTTGAACAT TCGCGACGGC AAGGCGGAAT ATGTTTATCC GCAATGAGTG GCGTAAAAAC 120

CAATAAAGAC AAATTTAGAT GATGTCGGGG AAGATGCCCG ACCGACAAGA CTATGCAAAA 180

TATGAAAAAC CAAGTACGCG GATCAGGCAT GGATGCACGA TCCAATCCG 229

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 207 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

CGGGTCGCTT TATTTTGTGC AGGCATTATT TTTCATTTTT GGCTTGACAG TTTGGAAATA 60

TTGTGTATCG GGGGGGGGTA TTTGCTGACG TAAAAAACTA TAAACGCCGC GCAAAATATG 120

GCTGACTATA TTATTGACTT TGATTTTGTC CTGCGCGGTG ATGGATAAAA TCGCCAGCGA 180

TAAAGAATTT GCGAGAACCT GATGCCG 207

(2) INFORMATION FOR SEQ ID NO: 81 :

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 224 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

CGGCAACGAT TTGAGCTATC GCGGTTACGA CATTCTGGAT TTGGCACAAA AATGCGAGTT 60

TGAAGAAGTC GCCCACCTGC TGATTCACGG CCATCTGCCC AACAAATTCG AGCTGGCCGC 120

TTATAAAACC AAGCTCAAAT CCATGCGCGG CCTGCCTATC CGTGTGATTA AAGTTTTGGA 180

AAGCCTGCCT GCACATACCC ATCCGATGGA CGTAATGCGT ACCG 224

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 212 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

CGGGAACAGC CATTGCCCAC GCCCACGCCC CCCAAGAAAG ACGGAAACTA CTGCCTAAAT 60

TTTCGGCAAT CAAGTTGACG ATTAAAGGGT TGGGGGCAGT TGCAGTAATA AACATAGCCG 120

ACGAAATGGG ATTGGAATGA TAGTTGACCA AAGCCAAATA TTTACCCATC TTGCCTTCTG 180

TGCCTTTTGC GGGATTGGAG CCGTAACTGC CG 212

(2) INFORMATION FOR SEQ ID NO: 83

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 353 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83

CGGGAATTCT GAGCAGAATG AAAGAAAGCA GGCTTGATAA TTTCATAAAG TTATTGGAAG 60

AAAAAGGATT TACCGTCCAT TTCGGTATTC ACAATACGGC TGATTACGGA ATTCCCCAAA 120

GCCGTAAAAG ATTTACGTTA ATTGCAAACA GAATAACCAA AGAAAAGCTG GAACCAGTCA 180

AGTATTCGGG CAAACGGCTT ACGGTAGCCG ATGTTTTGGG AATGGAAATG GCTTTCCCAA 240

CATTATTGCA GGACACCAAG ACGAAACGGA TTTTATGCAT AGCTGTGCGG GAATTATCTG 300

ATATCACTTG AACGATTGGC TTGATACCTA AAAACGGAGG AACCGTTGGC TTT 353

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

AATTCCGTAT CCAAACTTTG CGGGTTAGAT AAAGGGGTGT AGTCTGTCCC GCTTATGGTA 60

ACGCTGTCGC GGCGGACTAC GCCCGGAGCC TTTTTCCAGT AAGTTTTCGG AAATCAGGCT 120

GTGGGTGGTT TTTAAGAAAT CCAACCAGTC AAACGGCTCG GGGCTGTCCA AACCGGACAC 180

AGGTGCCGGT AACTTTCCCT CAGGTTGATT AACATTACGG CATCCGAATA TAACTTCCCG 240

CCTGCGGTTT GCCCGAGTTT AAGCAATGCC TGCGTATCGT ATTGATTATA AAGTGTTTCC 300

TTCCAATT 308

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 104 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

AATTCGTGTG CCGCGTCGAC AAACCGCTGA CGTAGCGGAT GTCTCATGCC ACGTTTCAAA 60

GCAGGTTGAT GGCGGTTAGC AACCCTCTGA TTTCACTGGG ATAT 104

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 89 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

AATTGCGTAG AGTGGGCTTC AGCCACGTTT TTTCTTTTTC GGTCGTTGAT TGGTGGGCTG 60

AACCACTTGT TTCGGAAATC CGTATCATG 89

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 273 base pairs
(B) TYPE: nuclectide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

AATTTCCACC TATGCCCTAC GCAGCGATTA TCCGTGGTTT ACCCAAAGGG TGATTATGGC 60

AAAAGCGCGG GGTTGAGCGA CCGCCTTTTG TTGCCGGCGT TCAAACGGGT TTTGATAGGA 120

AATGCAGGCA CGAAGCCTCG GCTGATTGTG ATGCACCTGA TGGGTTCGCA CAGTGATTTT 180

TGCACACGTT TGGATAAGGA TGCGCGGCGG TTTCAGTATC AAACTGAAAA AATATCCTGC 240

TATGTTTCCA TCAATCGCGC AAACCGATAA ATT 273

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 270 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

AATTCTTCCG CACGGGGAGG CTTGTTTTTC TTCCCTTCTG TTCCGACCGA TTCTCAAATA 60

AAAATCATTG ATTTCATCGA AGTTCATTCC TATACCATTA TCTTTAATAA CGATTTTATG 120

CTCCGGTTTA TCGAATAACC TAACTTCCAC TTCCGTAGCA CATGCATCGT AGGCATTCGC 180

TATCAACTCG GCAATCGCAG GAACAGTGTG CGAATACAAT CTTTACACCC AAATGTTCGA 240

TTACGGTTGG CTCGAAACTC AATTTCAATT 270

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 267 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

AATTATGAAC ACACGCATCA TCGTTTCGGC TGCGTTCGTT GCGTTGGCAT TAGCAGGTTG 60

CGGCTCAATC AATAATGTAA CCGTTTCCGA CCAGAAACTT CAGGAACGTG CCGCGTTTGC 120

CTTGGGCGTC ACCAATGCCG TAAAAATCAG CAACCGCAGC AATGAAGGCA TACGCATCAA 180

CTTTACCGCA ACTGTGGGTA AGCGCGTGAC CAATGCTATG TTACCAGTGT AATCAGCACA 240

ATCGGCGTTA CCACTTCCGA TGCAATT 267

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 234 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

AATTTTTATT TGGTTCGTAG TCATTTTGTG CAACTGAACG ATATTCGTTT TCATCATTGC 60

TAACGTCTAG TGCCCATTGT GGCCCGTAAT AAGAGATTTC GTCTCCTTTT ACATGTTTGA 120

CGCTGACGGC ATACTGGGGA TCGATGACGG ATAATGTACG TCTGTTGACA TCTGCAACGC 180

TAAATCAATC ATCGGTATTG GATAATGCGT TGCCGATGTT TTGACTTGTA TGTT 234

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 295 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

AATTCGGCCG GCTGTGTCAA ATAATGCGTT ACTTTGGCCG GGTCTTGTTC TTTGTAAGTG 60

GTGGTCTTTT TTTGCGCGTT ATCCCCATCT GTTTGAGTGC ATAGCAAATG GTGGCTGCCG 120

TACAATCAAA TGTTTGGCGT TCATGCAGAT AGGCATCATG GTGTTGCCCA ATATATTGAG 180

CCGGTTTTTG CCTATCCGAT TTGACGGCAT TTAGACCGGT AACTTGATGT TTTAAGCTGC 240

CTGTTTGTTT AAAGGCGAAT CCACAAGTAA AGCGTGTTTC TTGACAGGTT AAACG 295

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 259 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

AATTGTGTAT ATCAAGTAGG ATGGGCATTT ATGCCTGACC TACAAAACCA AAAACAACCT 60

ACCACCCTTA ATCAACTCCA CAAACCCTCT TCAGACAACC TCGTTTTTTG AAAAACAATC 120

TGTAAACAGA TAACTGCTGA AGAATACCGT TGCCGAGCCC CAAAACCCGT ACTGCAACTT 180

TTATTGTGAA CTTCCCATTA TGAGAAAATC CCTTTTCGTC CTCTTTCTGT ATTCGTCCCT 240

ACTTACTGCC AGCGAAATT 259

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 379 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

AATTGCACCA CGCGATGATG GGTACGCCTC TGTTGCCATT GCGACCGCCG CCGCCGTGCC 60

CGGTACGCTG GTCAACCTTG CCGCGGCGGA ACGGGTAAAG AAGTGCGCTT CGGGCATCCT 120

TCCGGTACAT TGCGCGTCGG TGCAGCGCCG AATGTCAGGA CGGACAATGG ACGGCCACCA 180

AAGCGGTTAT GAGCCGCAGC GCACGCGTGA TGATGGAAGG TTGGGTCAGG GTGCCGGAAG 240

ATTGTTTTTA AATTGGACGG CGAACCGGTC TATTCGTATT GGCGTTATAC CGCCGCAAAG 300

GCAGACCTTG AAACTGGTGC GTGCCGTGCA GGGCATGTAC GGCTATGTGT GCGTGGCGGG 360

CGGATTTGAT GTGCGGAAT 379

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

AATTTGTTGG GCAGATGGCC GTGAATCAGC AGGTGGGCGA CTTCTTCAAA CTCGCATTTT 60

TGTGCCAAAT CCAGAATGTC GTAACCGCGA TACGTCAAAT CGTTGCCGGT ACGCAACGGT 120

ACACAAAGCG GTATTACCGG CCGCAACGCC AGAAAGCGCA ACGGATTTTT AGGTTTGAGG 180

GTCGGGGTTT GAGTAGTTTC AGTCATGGTA TTTCTCCTTT GTGTTTTTAT GGGTTTCGGG 240

TTTTCAGACG ACCGATGCGG ATTTGTTGAA AGGCAGTCTG AAAGCGGTAA ATCATTTTTG 300

AAACAATT 308

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 286 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

AATTCGGAGG AGCAGTACCG CCAAGCGTTG CTCGCCTATT CCGGCGGTGA TAAAACAGAC 60

GAGGGTATCC GCCTGATGCA ACAGAGCGAT TACGGCAACT TGTCCTACCA CATCCGTAAT 120

AAAAACATGC TTTTCATTTT TTCGGCAAGC AATGACGCAC AAGCTCAGCC CAACACAACT 180

GACCCTATTG CCATTTTATG AAAAAGACGC TCAAAAAGGC ATTATCACAG TTGCAGGCGT 240

AGACCGCAGT GGAGAAAAGT TCAATGGCTC CAACCATTGC GGAATT 286

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 238 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

AATTTGGATA CGTTGGAAAA GGGATATTTG ATTGGGAATG GGATGAAGAT AAGCGTAGAT 60

GAGTTGGGGA AAAAAGTGTT AGAACATATC GGTAAGAATG AACCGTTATT GTTGAAAAAT 120

CTACTGGTTA ACTTCAATCA GGGAAAACAT GAAGAAGTTA GGAAGTTGAT TTATCAGTTG 180

ATAGAGTTAG ATTTTCTGGA ACTTTTGTGA GGGATTCTAT GAAAAACTGG AAGCAATT 238

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 322 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

AATTCGGCAC GCAGGTTTTC TAAAAAAAGG CCGTTGATGA CTTTGTCGAT ATTGGCGGCT 60

TCGGTGTAGT GCGCGCCCGC TTCGGCCGCT CTTGCGCGTC CATGACGGAT TGGAAGAGCG 120

TGCCGAAGAT TTCTGGACTG ATGTTGCGCC AGTCGAAATT GCCGACACGG GAGGAATACC 180

TGCCAACAAG AGTGCAGGCA GCGTAATCAA ACCACCCCCA CCCGCAATCG CATCGATAAA 240

TCCGGCAATC ATCGCAACCA AACCCAAAGC GAGTATTATG TATAAATCTT CCATGTTTCT 300

TAATCCTGTT AACTTGCACC AA 322

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 316 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98

AATTTGTCGG CAATCTTCCC GGGTCGCTTT ATTTTGTGCA GGCATTATTT TTCATTTTTG 60

GCTTGACAGT TTGGAGATAT TGTGTATCGG GGGGGGGTAT TTGCTGACGT AAAAAACTAT 120

AAACGCCGCA GCAAAATATG GCTGACTATA TTATTGACTT TGATTTTGTC CTGCGCGGTG 180

ATGGATAAAA TCGCCAGCGA TAAAGATTTG CGAGAACCTG ATGCCGGCCT GTTGTTGAAT 240

ATTTTCGACC TGTAATTACG ATTTGGCTTC CGCGCCGGCA CAATATGCCG CCAAGCGGCG 300

CCCACATTTT GGAAGC 316

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 217 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

AATTCGGACA GTATGAATAC AGCGGATTAA TACAAGGTAA GTTCATTACA ACGGAAAAAC 60

CTTTAAAGAA TAATATGAAA GGTATTACCT TGTTTGCCAA CGGGAATGGT AAATATGCCC 120

GAGTTTTTCA CTGAATAGCG AATCCAGCCA TTTCTATTCA TATTTGACTG GATGGCTGAA 180

TGTGGACTTT ATAGATAATG ACGATGAAGA TTTAATT 217

CLAIMS

1/ DNAs, characterized in that they are in all or part genes, with their reading frame, present in *Neisseria meningitidis* (called Nm below), but absent both from *Neisseria gonorrhoeae* (called Ng below) and from Neisseria Pactamica [sic] (called Nl below), with the exception of genes involved in the biosynthesis of the polysaccharide capsule, *frp*A, *frp*C, *opc*, *por*A, rotamase, the sequence IC1106 [sic], IgA proteases, pilin, pilC, proteins which bind transferrin and opacity proteins.

2/ DNAs according to claim 1, characterized in that they are present in Nm, but absent from Ng.

3/ DNAs according to claim 2, characterized in that they comprise one or more sequence(s) present on the chromosome of Nm Z2491 between *tuf*A and *pil*T, or region 1 of the chromosome, and/or the nucleotide sequence(s) capable of hybridizing with the said sequence(s).

4/ DNAs according to claim 2, characterized in that they comprise one or more sequence(s) present on the chromosome of Nm Z2491 between *pil*Q and λ740, or region 2 of the chromosome, and/or the nucleotide sequence(s) capable of hybridizing with the said sequence(s).

5/ DNAs according to claim 2, characterized in that they comprise one or more sequence(s) present on the chromosome of Nm Z2491 between *arg*F and *opa*B, or region 3 of the chromosome, and/or the nucleotide sequence(s) capable of hybridizing with the said sequence(s).

6/ DNAs according to claim 3, characterized in that their sequence corresponds in all or part to SEQ ID No. 9, 13, 22 or 30, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or is

capable of hybridizing with at least a fragment of any one of these sequences.

7/ DNAs according to claim 4, characterized in that their sequence corresponds in all or part to SEQ ID No. 1, 2, 4, 6, 7, 10, 15, 31 or 34, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or is capable of hybridizing with at least a fragment of any one of these sequences.

8/ DNAs according to claim 4, characterized in that they are all or part of the DNA sequence SEQ ID No. 36 or sequences corresponding to the open reading frames SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45 and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or is [sic] capable of hybridizing with at least a fragment of any one of these sequences.

9/ DNAs according to claim 5, characterized in that their sequence corresponds in all or part to SEQ ID No. 8, 21, 23, 25, 26, 28, 29, 32 or 35, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or is capable of hybridizing with at least a fragment of any one of these sequences.

10/ DNAs according to claim 2, characterized in that their sequence corresponds in all or part to SEQ ID No. 3, 5, 11, 12, 14, 16, 18, 19, 20, 24, 27 or 33, and/or to any sequence located at more or less 20 kb from these SEQ ID on the chromosome of an Nm strain, and/or is capable of hybridizing with at least a fragment of any one of these sequences.

11/ DNAs according to claim 1, characterized in that they are common with those of Ng, but are absent from Nl.

12/ DNAs according to claim 11, characterized in that they comprise one or more sequence(s) present on the chromosome of Nm Z2491 between arg J and reg F, or region 4 of the chromosome, and/or the nucleotide sequence(s) capable of hybridizing with the said sequence(s).

13/ DNAs according to claim 11, characterized in that they comprise one or more sequence(s) present on the chromosome of Nm Z2491 between the marker lambda 375 to pen A, or region 5 of the chromosome, and/or the nucleotide sequence(s) capable of hybridizing with the said sequence(s).

14/ DNA according to any one of the preceding claims, characterized in that it codes for a protein exported beyond the cytoplasmic membrane.

15/ DNAs according to any only of claims 1 to 14, characterized in that all or part of their sequence corresponds to a region conserved within the Nm species.

16/ DNA according to any one of claims 1 to 15, characterized in that it is inserted in a transfer or expression vector, such as a cosmid, plasmid or bacteriophage.

17/ Host cell, more particularly bacterial cell or Nm cell, transformed by insertion of at least one DNA according to any one of claims 1 to 15.

18/ Cell comprising genes or gene fragments specific to Nm, more particularly bacterial cell or Nm cell, the chromosome of which is deleted by at least one DNA according to any one of claims 1 to15, in particular a DNA responsible for the pathogenicity.

19/ DNAs, characterized in that their sequence corresponds in all or part to the transcription of at least one DNA sequence or sequence fragment according to any one of claims 1 to 15.

20/ Antisense nucleic acids, characterized in that their

sequence corresponds to the antisense of at least one nucleotide sequence according to any one of claims 1 to 15 or 19, or a fragment of such a sequence, and in that they carry, where appropriate, at least one chemical substituent, such as a methyl group and/or a glycosyl group.

21/ Polypeptides, characterized in that they have an amino acid chain corresponding to all or part of a sequence coded by the nucleic acids defined in any one of claims 1 to 15 or 19, or deduced from sequences of these nucleic acids, with, where appropriate, modifications with respect to the coded or deduced sequences, where these modifications do not alter the biochemical properties observed in the natural polypeptide.

22/ Peptides according to claim 21, characterized in that they are peptides exported beyond the cytoplasmic membrane, more specifically peptides corresponding to all or part of those coded by a DNA according to claim 14.

23/ Antibodies, characterized in that they are polyclonal or monoclonal antibodies directed against at least one epitope of a peptide according to claim 20 or 21, or fragments of these antibodies, more particularly fragments Fv, Fab, Fab'2, or also anti-antibodies capable of recognizing, by a reaction of the antigen-antibody type, the said antibodies or their fragments.

24/ Process for obtaining *Neisseria meningitidis*-specific DNA banks, comprising

- mixing of two DNA populations,

- realization of at least one subtractive hybridization-amplification iteration, and

- collection of the desired DNA or DNAs, followed, where appropriate, by its/their purification with elimination of redundant sequences.

25/ Process according to claim 24, characterized in that, to obtain a bank which is specific to Nm, in contrast to Ng

- two DNA populations originating respectively from a strain of *Neisseria meningitidis*, or a reference strain, for which the specific bank is to be constructed, and a strain of *Neisseria gonorrhoeae*, or a subtraction strain, the DNA sequences of these strains being those obtained by

. - random shearing of the chromosomal DNA of the subtraction strain, in particular by repeated passage through a syringe, and

. cleavage of the chromosomal DNA of the reference strain, preferably by a restriction enzyme producing fragments less than about 1 kb in size, and in that to obtain a bank of DNAs common between Nm and Ng, but specific with respect to Ng, three different banks are constructed, two of them by digestion of the chromosomal DNA of Nm by *MboI* and *Tsp5091*, and the third by digestion of the chromosomal DNA of Nm with *MspI*, two subtraction series are carried out, and the DNAs having the required specificity are collected.

26/ Banks of DNA clones obtained by carrying out the process according to claim 24 or 25.

27/ Use of the process according to claim 24 to obtain banks of DNAs specific to a given cell or to a given variant of the same species of cell, where another species or another variant which is close genomically and expresses different pathogenic potencies exists, in particular banks of DNAs specific to cryptococci, Haemophilus, pneumococci or also Escherichia.

28/ Method for diagnosis of a meningococcal infection, and more particularly of meningococcal meningitis, by demonstration of the presence of *Neisseria meningitis* in a biological sample, characterized in that it comprises the

stages of:

- bringing into contact a biological sample to be analysed and a reagent formulated from at least one nucleic acid as defined in one of claims 1 to 15 or 19, if appropriate in the form of a nucleotide probe or a primer, or, as a variant, from at least one antibody or a fragment of an antibody, as defined in claim 23, under conditions which allow respectively hybridization or a reaction of the antigen-antibody type, and

- detection of any reaction product formed.

29/ Method for diagnosis of an immune reaction specific to meningococcal infection, characterized in that it comprises the stages of:

- bringing into contact a biological sample to be analysed and at least one polypeptide according to any one of claims 21 or 22 or an anti-antibody according to claim 23, or a fragment thereof, these products being labelled, where appropriate, under conditions which allow a reaction of the antigen-antibody type to be effected, and

- detection of any reaction product formed.

30/ Kits for carrying out a method according to any one of claims 28 or 29, characterized in that they comprise

- at least one reagent as defined in claim 28 or 29, that is to say of the nucleic acid, antibody or peptide type,

- products, in particular markers or buffers, which enable the intended nucleotide hybridization reaction or immunological reaction to be carried out, as well as use instructions.

31/ Vaccine composition including in its spectrum, in particular in combination with at least one childhood vaccine, antimeningococcal prophylaxis and intended for prevention of any form of infection by *Neisseria meningitidis*, characterized

in that it comprises, in combination with (a) physiologically acceptable vehicle(s), an effective amount:

- of peptide according to claim 21 or 22, or

- of antibody or anti-antibody fragment according to claim 23,

this material optionally being conjugated, in order to reinforce its immunogenicity, with a carrier molecule such as a poliovirus protein, tetanus toxin, protein produced by the hypervariable region of a pilin.

32/ Vaccine composition including in its spectrum, in particular in combination with at least one childhood vaccine, antimeningococcal prophylaxis and intended for prevention of any form of infection by *Neisseria meningitidis*, characterized in that it comprises, in combination with (a) physiologically acceptable vehicle(s), an effective amount:

- of nucleic acids according to any one of claims 1 to 15 or 19 or

- of cells according to claim 17 or 18.

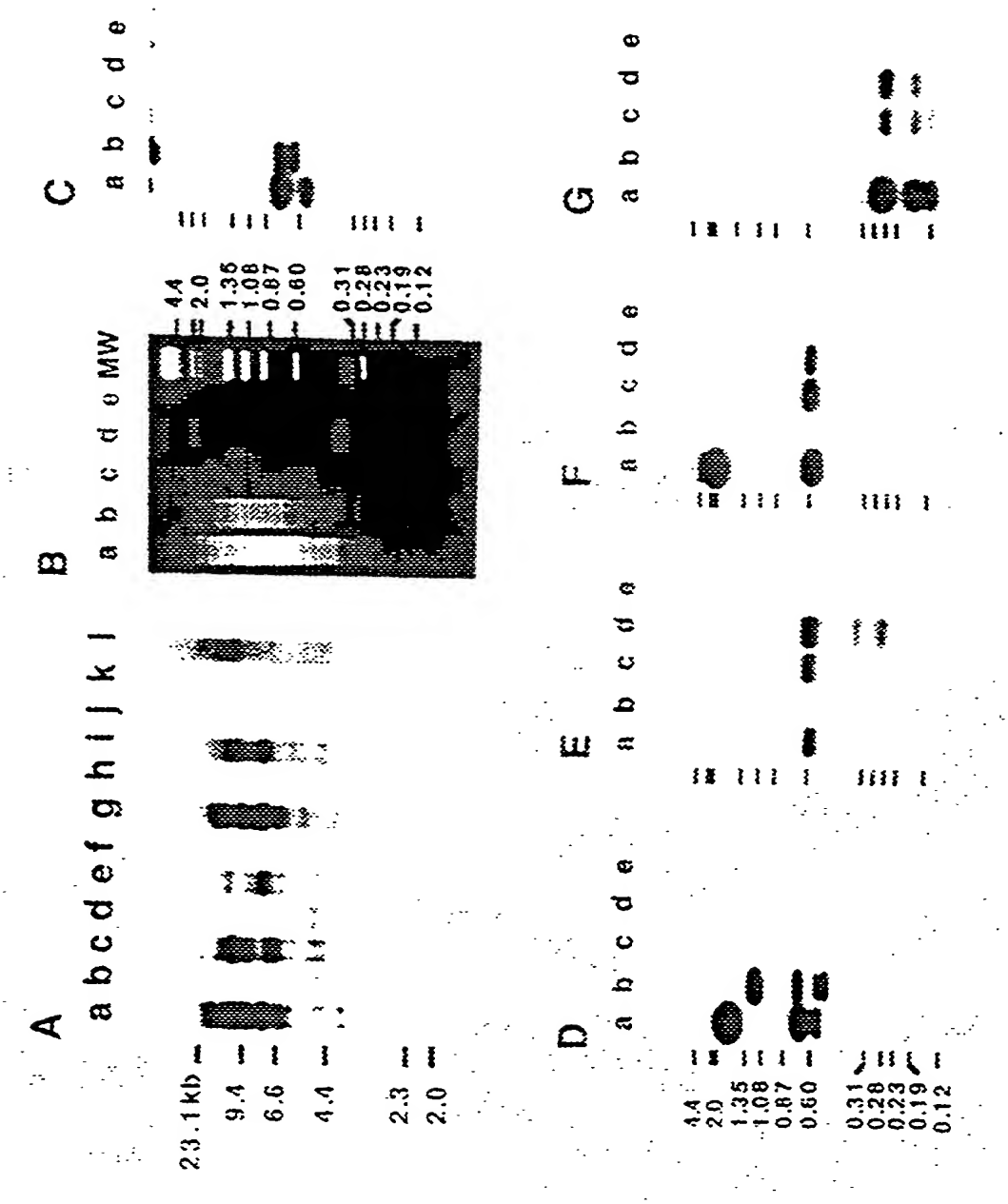
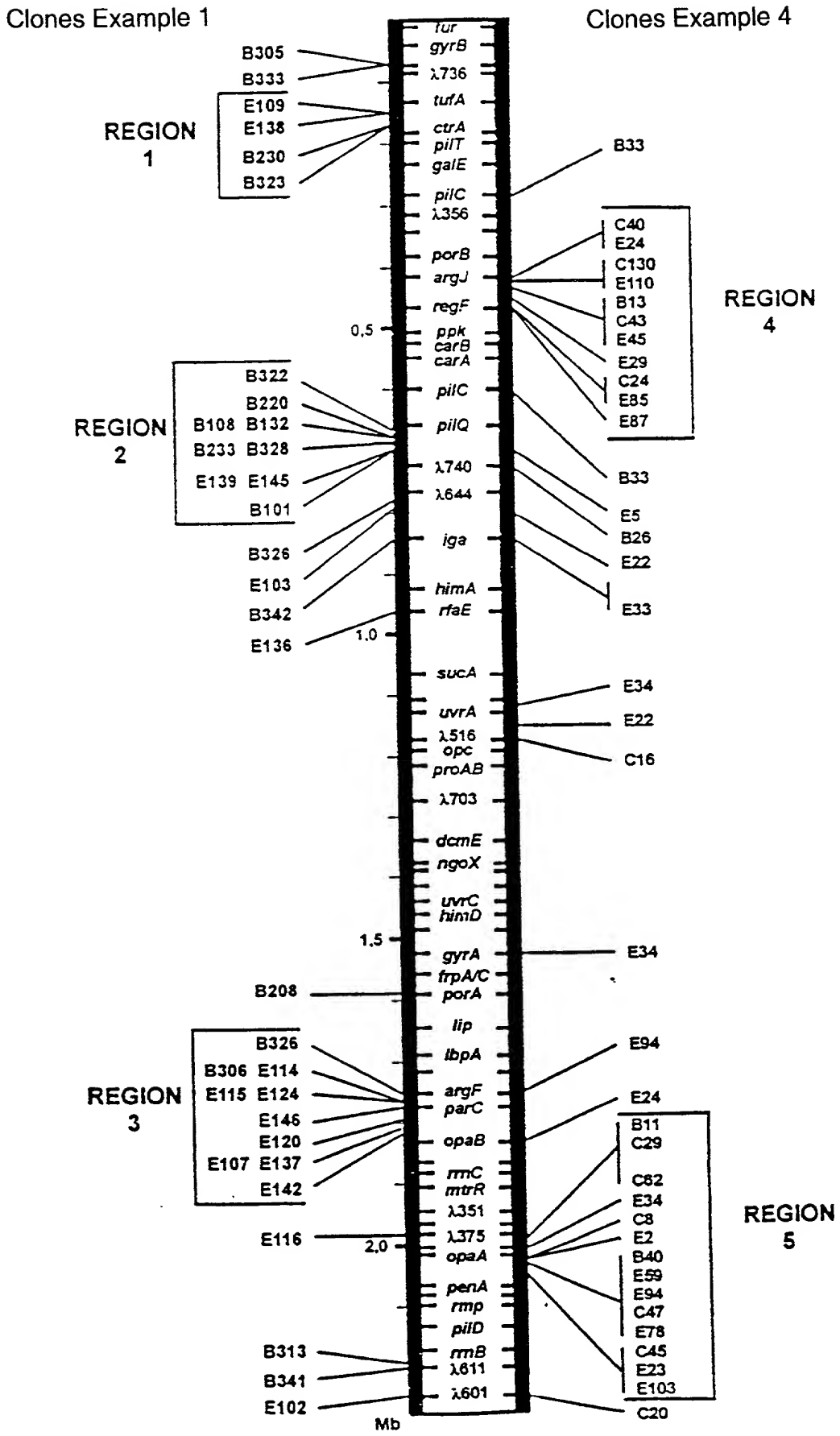
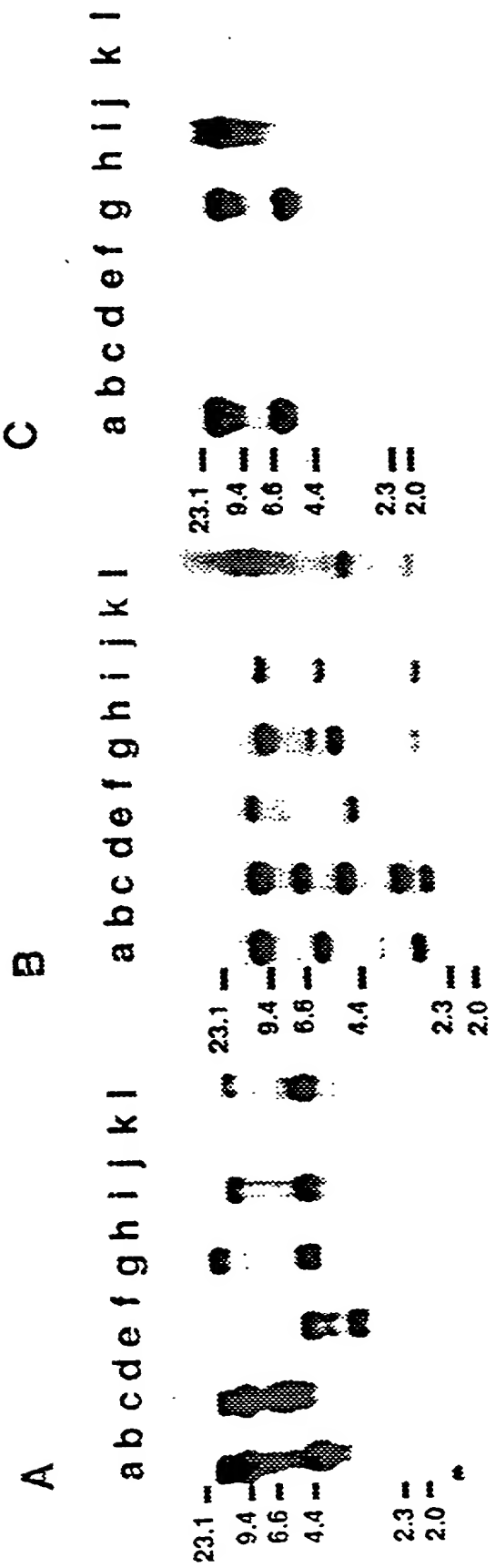


Figure 2





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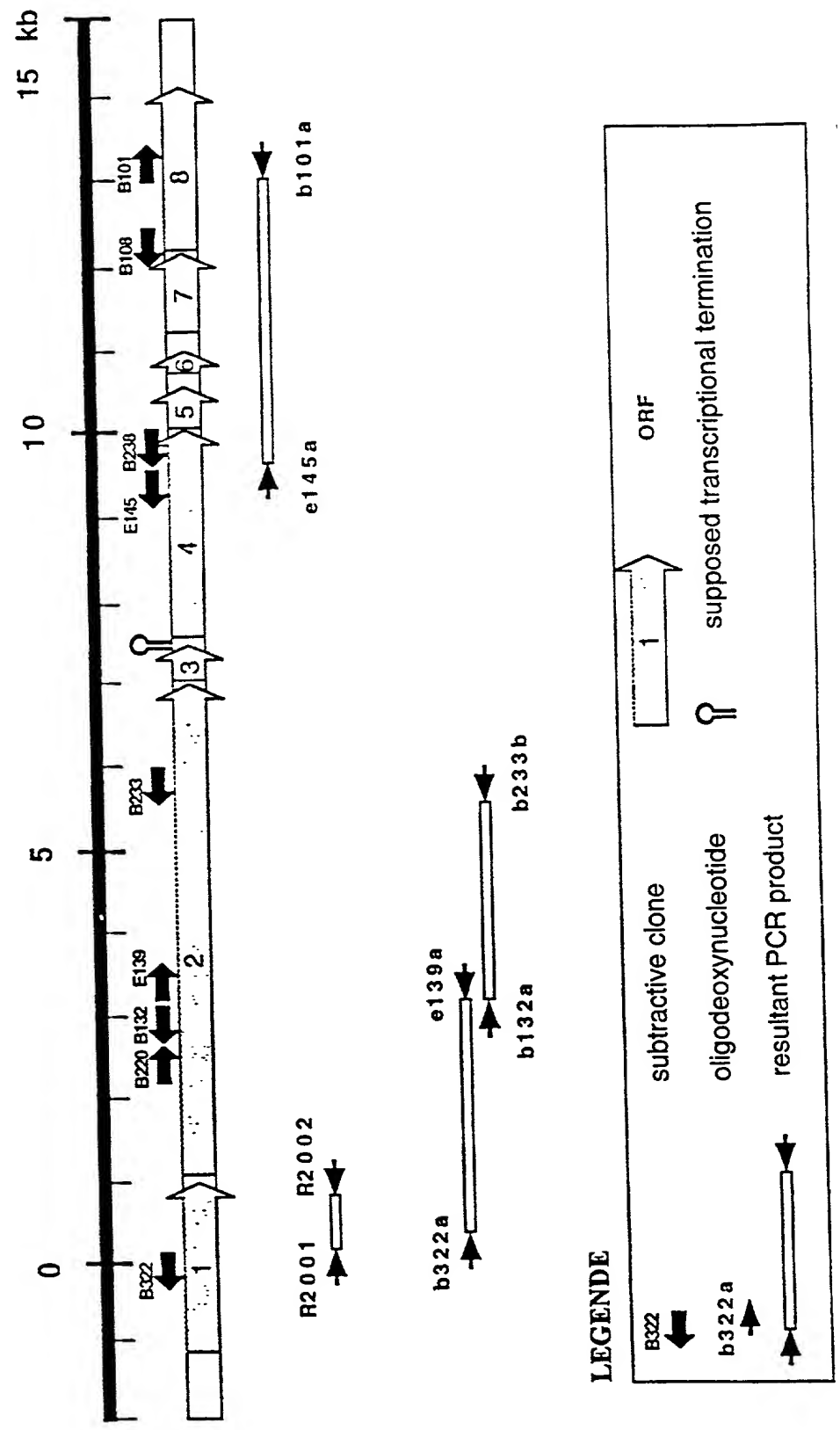
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e145a
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b233b
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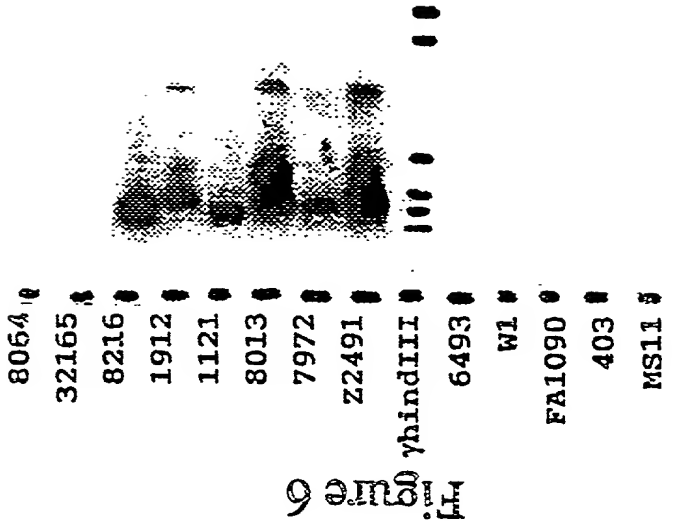
subtractive clone
oligodeoxynucleotide
resultant PCR product
ORF
supposed transcriptional termination



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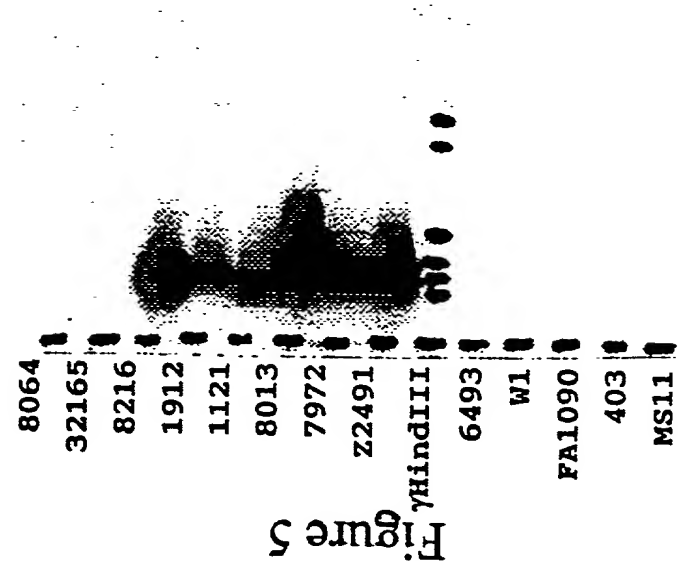


Figure 5

Figure 7

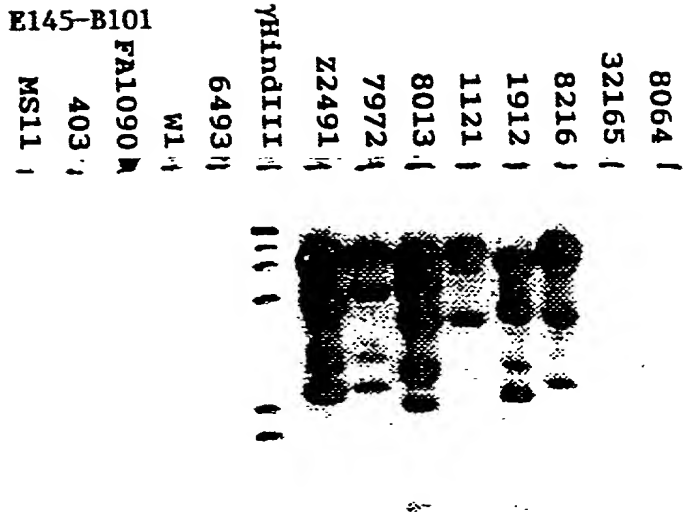


Figure 8A

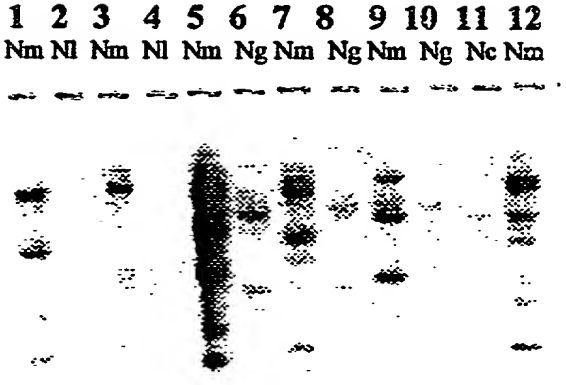


Figure 8B

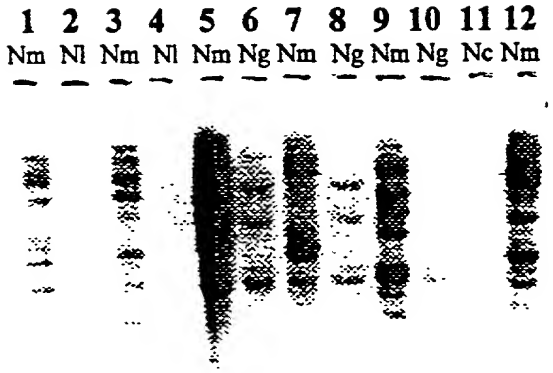
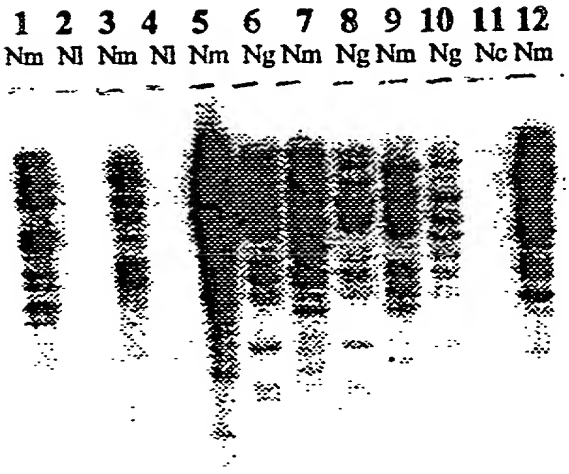


Figure 8C



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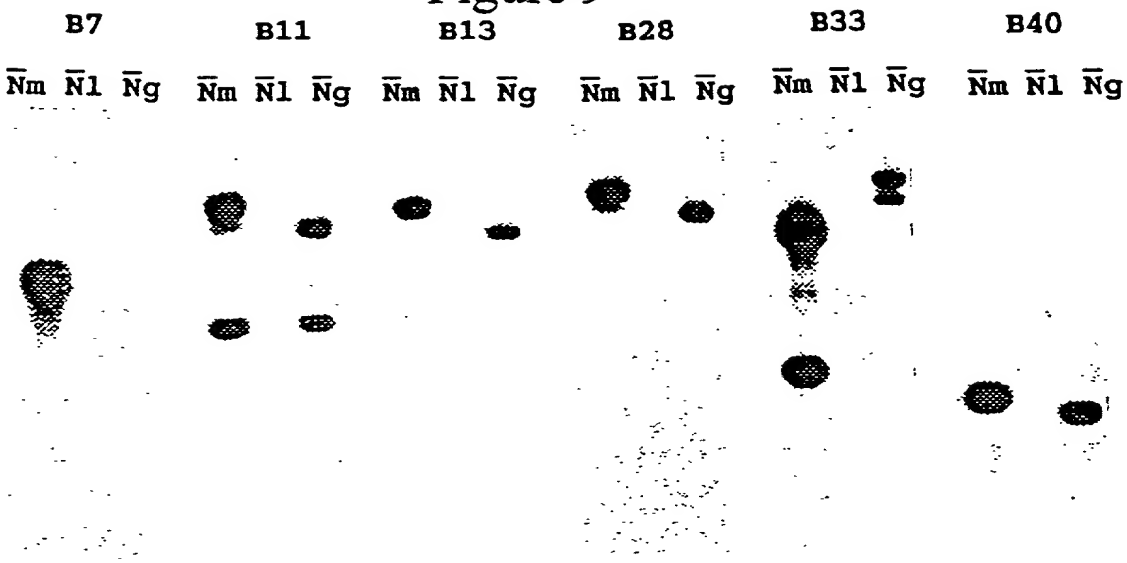


Figure 10

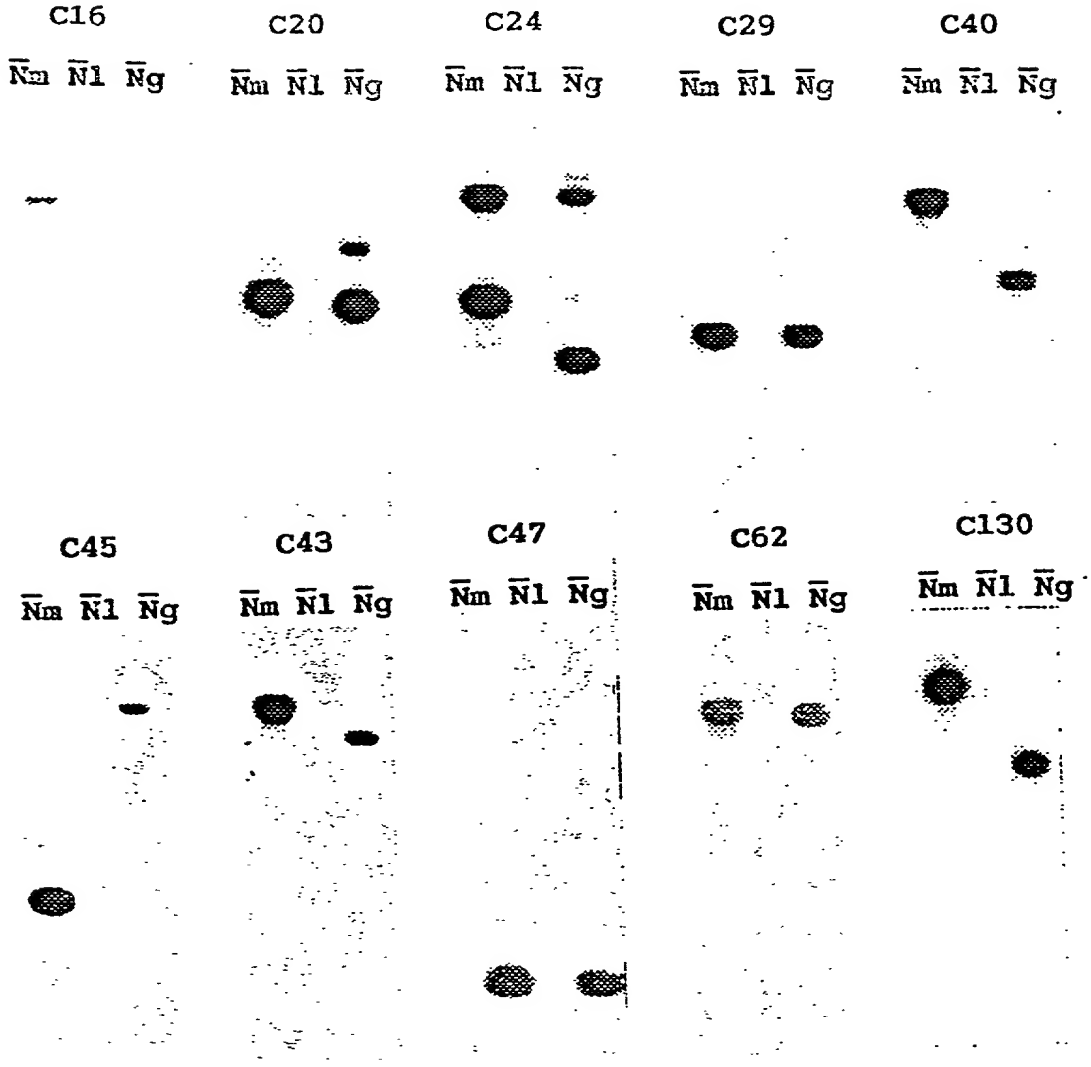
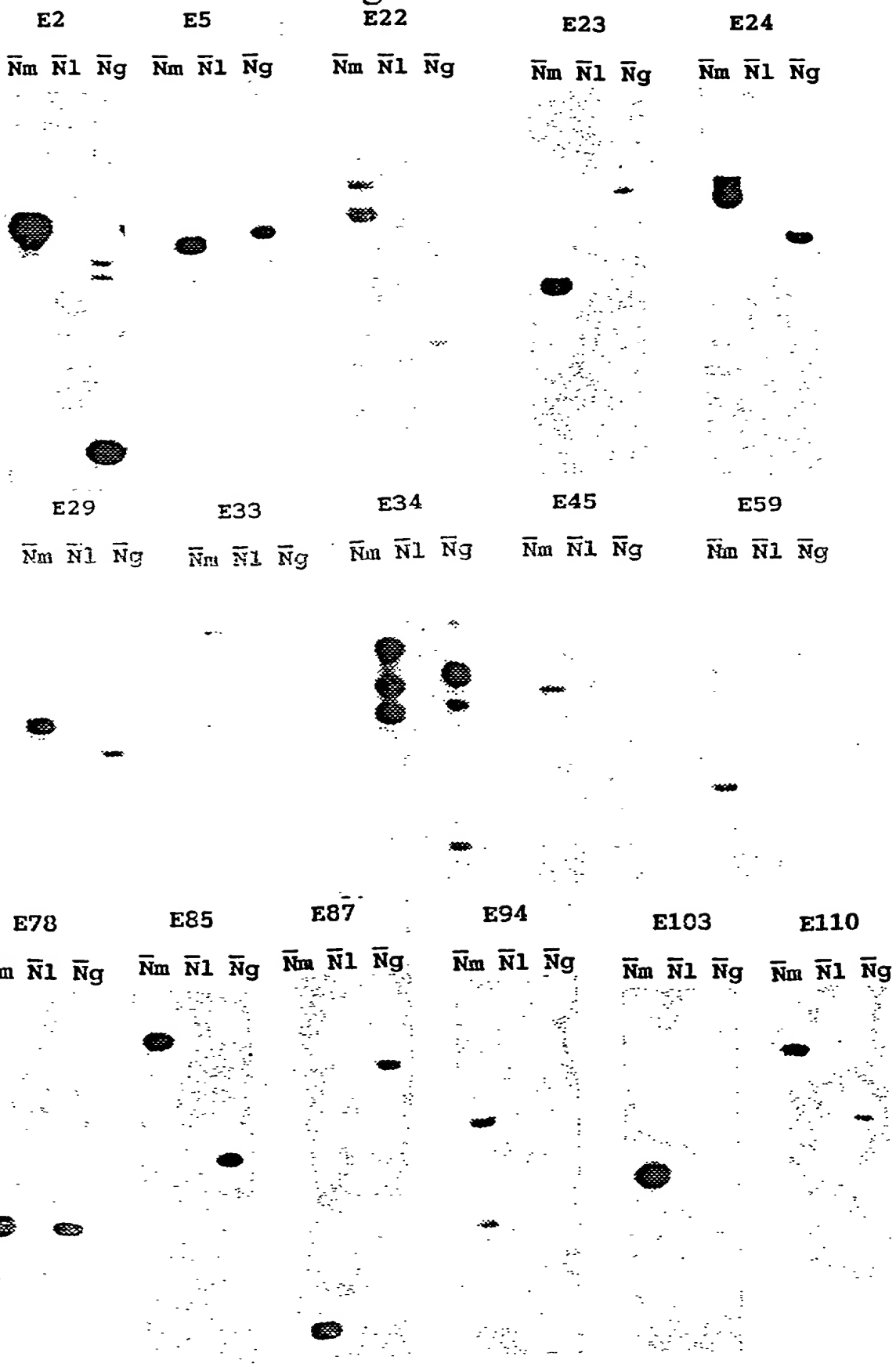


Figure 11



RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: "DNA and proteins or peptides specific of bacteria of the Neisseria meningitidis species, methods for obtaining them and biological applications thereof".

the specification of which (**check** applicable **box(s)**):

[ ] is attached hereto.

[ ] was filed on _____ as U. S. Application Serial No. _____.

[X] was filed as PCT international application No. PCT/ FR 97/01295 on July 11,1997.

and (if applicable to U.S. or PCT application) was amended on _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:

Prior Foreign Application(s):

Application Number	**Country**	**Day/Month/Year Filed**
96 08768	FR	12/07/1996

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior applications in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

Prior U.S./PCT Application(s): Application Serial No.	**Day/Month/Year Filed**	**Status: patented, pending, abandoned**
PCT/FR 97/01295	11/07/1997	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed)**, and the following attorneys thereof (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Arthur R. Crawford, 25327; Larry S. Nixon, 25640; Robert A. Vanderhye, 27076; James T. Hosmer, 30184; Robert W. Faris, ~~34352,~~ Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H. Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Paul J. Henon, 33626; Jeffry H. Nelson, 30481; John R. Lastova, 33149; H. Warren Burnam, Jr., 29366; Thomas E. Byrne, 32205; Mary J. Wilson, 32955; J. Scott Davidson, 33489; Jerry D. Craig, 38026.

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